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«Healthy Medicine»

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Korrespondenz/Correspondance
SGIM, Schweiz. Gesellschaft
für Allgemeine Innere Medizin
Solothurnerstrasse 68
Postfach
4002 Basel
jahresversammlung@sgim.ch

HUBER

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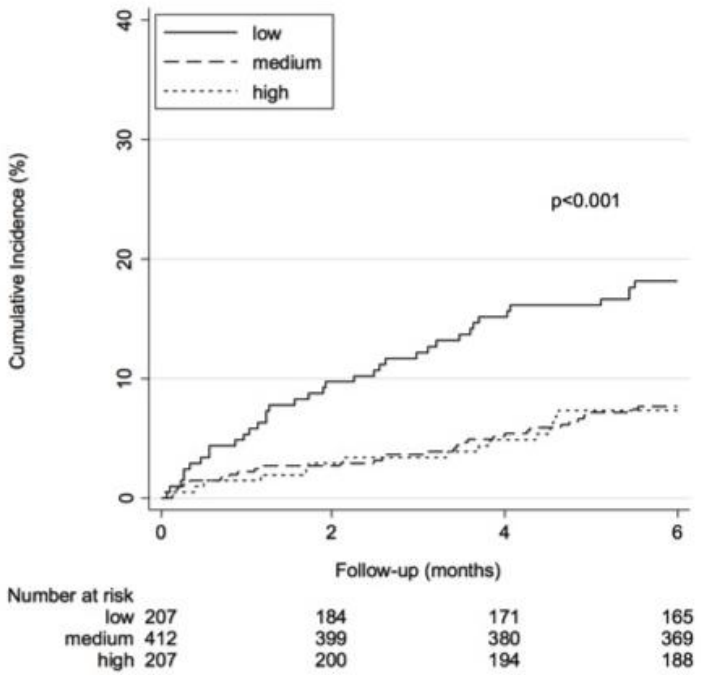
FM248 Whole blood omega-3 fatty acid content predicts recurrent venous thromboembolism and death in elderly patients with acute venous thromboembolism

Martin F. Reiner[1,2], Simona Stivala[1,2], Andreas Limacher[3], Sara Gobbato[1,2], Marie Méan[4], Nicolas Rodondi[4], Drahomir Aujesky[4], Clemens von Schacky[5], Thomas F Lüscher[1,6], Giovanni G. Camici[1], Jürg H. Beer[1,2]

[1]Laboratory for Platelet Research, Center for Molecular Cardiology, University of Zurich, Schlieren, [2]Department of Internal Medicine, Cantonal Hospital Baden, Baden, [3]Clinical Trials Unit Bern, Department of Clinical Research, and Institute of Social and Preventive Medicine, University of Bern, [4]Department of General Internal Medicine, Bern University Hospital, Inselspital, Bern, Switzerland, [5]Omegametrix GmbH, Martinsried, Germany, [6]Department of Cardiology, University Heart Centre, University Hospital Zurich, Zurich, Switzerland

Background: Venous thromboembolism (VTE) is a leading cause of cardiovascular disease (CVD) and death. Omega-3 fatty acids (n-3 FA) have been shown to reduce the risk of CVD and mortality due to their antiinflammatory and antithrombotic properties. Inflammation, platelet activation and coagulation are key mechanisms of VTE. Elderly patients with previous VTE are at particular risk for recurrent VTE due to their frequent proinflammatory and prothrombotic comorbidities. We therefore hypothesized that increased n-3 FA are associated with a lower risk of recurrent VTE and death in elderly patients with previous VTE.
Methods: We determined baseline whole blood FA composition by gas chromatography in 826 patient samples from The Swiss Cohort of Elderly Patients with VTE (SWITCO65+), a prospective multicenter cohort study of in- and outpatients aged ≥65 years with acute VTE. We categorized n-3 FA into low, medium, and high levels based on the 25th and 75th percentile (low: 2.7 - 4.9%, medium: 4.9 - 6.6%, high: 6.6 - 11.6%). Associations between n-3 FA and the primary composite endpoint of recurrent VTE or death and the secondary endpoint of major and non-major bleeding within six months were assessed by ordinary Cox-regression and competing risk regression, respectively. Cumulative incidences of recurrent VTE or death and bleedings were estimated by the Kaplan-Meier method and compared using the logrank test. Recurrent VTE or death was adjusted for age, gender, overt PE, cancer, heart failure, chronic lung disease, BMI, provoked VTE, prior VTE, and periods of anticoagulation. Bleeding was adjusted for age, cancer, history of major bleeding, overt PE, antiplatelet therapy, and periods of anticoagulation.
Results: The cumulative incidence of recurrent VTE or death was significantly different among levels of n-3 FA ($p < 0.001$) (Fig. 1). A high level of n-3 FA was significantly associated with a reduced risk of recurrent VTE or death after six months (adjusted HR for high versus low level: 0.36, 95% confidence interval 0.20-0.67, p=0.001). In contrast, n-3 FA were not associated with major and non-major bleeding.
Conclusion: Our findings demonstrate that increased levels of whole blood omega-3 fatty acids are strongly associated with a reduced risk of recurrent VTE or death from any cause in patients with previous VTE. Anti-inflammatory and anti-coagulant mechanisms may mediate this effect. Total n-3 FA was not associated with risk of major and non-major bleedings.

Figure 1. Cumulative incidence of recurrent VTE or death by level of n-3 FA.



[Fig. 1]

FM249 **Does D-dimer predict recurrence of venous thromboembolism in elderly patients?**

Tobias Tritschler[1], Marie Méan[1,2], Andreas Limacher[3], Nicolas Rodondi[1], Drahomir Aujesky[1]
[1]Inselspital, Bern University Hospital, Bern, [2]Lausanne University Hospital, Lausanne, [3]University of Bern, Bern, Switzerland

Background: Evidence suggests that in patients with acute unprovoked venous thromboembolism (VTE), D-dimer levels measured after discontinuation of anticoagulation are associated with recurrent VTE. Although elderly patients with VTE have both a higher rate of VTE-related complications and higher D-dimer levels, no study has specifically examined whether there is an association between D-dimer levels and VTE recurrence in elderly patients.
Methods: We prospectively followed-up 268 patients aged ≥65 years with acute, symptomatic VTE from 9 Swiss university and non-university hospitals (09/2009-12/2013). All patients underwent quantitative D-dimer testing (ELISA, VIDAS®, bioMérieux, France) 12 months after the index VTE after having previously completed a 3 to 12-month course of anticoagulation. The outcome was the recurrence of symptomatic, objectively confirmed VTE occurring after D-dimer measurement. A committee of three blinded clinical experts adjudicated the outcome. We examined associations between log-transformed and dichotomized D-dimer values (cutoff 500 µg/L as proposed by manufacturer) and the time to VTE recurrence using competing risk regression, accounting for non-VTE-related death as a competing event. We adjusted for age, gender, type of VTE (provoked, unprovoked or cancer-related), localization of VTE and periods of anticoagulation as a time-varying covariate.
Results: The median age was 74 years and 44% of patients were women. VTE was unprovoked in 59%, 12% of patients had active cancer. Median follow-up was 23.4 months. Overall, 15% of patients had recurrent VTE and 7.5% died during follow-up. There was a significant association between quantitative

D-dimer levels and VTE recurrence (adjusted sub-hazard ratio [SHR] per log-unit increase 1.85; 95% confidence interval [CI] 1.08-3.18; P=0.026), but not between dichotomized D-dimer levels and VTE recurrence (adjusted SHR for < 500 µg/L versus ≥500 µg/L 0.65; 95% CI 0.26-1.65; P=0.367).
Conclusions: In our prospective multicenter cohort study including elderly patients with predominantly unprovoked VTE, we observed a significant association between quantitative D-dimer levels and recurrent VTE. However, D-dimer was not useful in predicting recurrent VTE using the usual test cut-off value (500 µg/L).

FM250 The role of code status in the triage of hospitalized seriously ill patients to intensive care: a qualitative study of internists' and ICU doctors' experiences

Monica Escher, Stéphane Cullati, Mathieu Nendaz, Bara Ricou, Patricia Hudelson, Thomas V. Perneger, Pierre Dayer
Hôpitaux Universitaires de Genève, Genève, Switzerland

Aims: The decision whether or not to admit a seriously ill patient to intensive care is complex. Code status is supposed to help doctors who do not know the patient to make a decision. We explored internal medicine (IM) and intensive care (ICU) doctors' experiences about the role of code status during the decision making process.
Methods: Individual, in-depth interviews with 12 IM and 12 ICU doctors. Doctors reflected on their experiences of ICU admission decision making. The analysis uses a thematic approach and focuses on code status as a factor influencing the process.
Results: Determination of code status is based on patient preferences, assessment of the context, and preferably on discussions with other colleagues. Code status is considered a core facilitator in the triage process, especially at night and during the week-end. Both IM and ICU doctors expect the doctor in charge to routinely discuss goals of care and to decide on a code status. When the admission decision is not straightforward, doctors meet with difficulties when there is no code or when the code is discrepant with their assessment of the clinical situation during the acute event. When the patient is full code, going against the instruction is perceived to be difficult for three reasons:
1. the referring IM and the ICU doctors make a far-reaching decision for a patient they do not know
2. the doctor caring for the patient probably decided on the code after careful consideration
3. intensive care is the patient's only chance of survival.

Strategies to solve the associated tension are:
1. reliance on the ICU doctor's expertise
2. collaborative decision making to reach a consensual decision
3. recognition that questioning the code status is legitimate
4. reliance on an a priori consensus about situations when ICU is justified (default decision in the absence of a code, acute event linked to iatrogenicity, certain diseases such as malignant hemopathies).

Conclusions: Code status is central to the time-pressured decision making about admission of a seriously ill patient to intensive care. Doctors feel uncomfortable when it is absent or discrepant with their clinical assessment during the acute event. Goals of care should be defined and clearly documented to substantiate and complement a patient's code status.

FM251 Perception of hospital autopsies by polymorbid patients: first results of a representative survey

Iljas Rosenberg, Burkhard Gierer, Renata Flury, Peter E. Ballmer
Department of Medicine, Kantonsspital Winterthur, Winterthur, Switzerland

Background: The number of autopsies in the hospital has been declining for decades, all over the world. In 1999 the autopsy rate was about 10% of patients dying in the hospital in Switzerland. Currently an autopsy frequency of about 2-3 % is assumed, but reliable data are not available. A further decrease in the autopsy rate might create substantial problems in the future, since the education of pathologists and clinicians might

be in danger. Moreover, adequate mortality registries can hardly be obtained without a certain number of autopsies. One possible reason for this negative trend is the appalling attitude of the population towards autopsies, which is at least in part triggered by the boulevard press and television.
Methods: A structured questionnaire was developed to investigate the attitudes towards autopsy of polymorbid patients in the department of medicine at the Kantonsspital Winterthur. This questionnaire is divided into 2 parts. The first part contains general information about age, sex, nationality, religion and education of the patients. In the second part, we developed 12 questions about the personal view of the patients in regard to purpose, experience and acceptance of performing an autopsy. Polymorbid patients were defined as patients with either a metastatic cancer or one active main diagnosis and 2 or more active secondary diagnoses.
Results: We interviewed 49 patients. The average age was 68,8 ± 15,2 years. 44 (89,8%) patients were willing to complete the survey anonymously. 25% of the patients suffered from metastatic cancer, 18.3% from cardiac disease, 22.4% from infectious disease,and 35% from other diseases (main diagnosis). 43% of the responding patients have been thinking about the procedure of an autopsy. There were 36% of the patients who accompanied a relative during the process of dying in hospital once in their life time. Only three of them have been asked by the medical staff, whether they would agree upon an autopsy after death of the relative. In total, 89% of the answering patients generally accepted hospital autopsies and 75% would agree to an autopsy on their own.
Conclusion: In summary, our data show that the present polymorbid patients predominantly have a positive attitude towards autopsy. Therefore, the decline of autopsy rates must have different reasons. In our view an important reason might be the negative attitude of the medical staff towards the autopsy, a hypothesis which we are currently investigating.

Freie Mitteilungen SGIM: Psychiatrie / Neurologie Endokrinologie/Diabetologie / Onkologie/Notfallmedizin / Nephrologie Arterieller Bluthochdruck

Communications libres SSMI: Psychiatrie / Neurologie / Endocrinologie Diabétologie / Oncologie/Urgences / Néphrologie / Hypertension artérielle

FM252 Prevalence of lab screening based type 2 diabetes mellitus in apparently healthy elderly from the Swiss Plateau

Pedro Medina Escobar[1], Lorenz Risch[2], Martin Risch[3], Urs Ernst Nydegger[4], Zeno Stanga[5]
[1]Klinische Chemie, [2]Hämatologie, Labormedizinisches Zentrum Dr. Risch, Liebefeld, [3]Zentrallabor, Kantonsspital Graubünden, Chur, [4]Haematology, Labormedizinisches Zentrum Dr. Risch, Liebefeld, [5]Department of Endocrinology, Diabetes and Clinical Nutrition, Bern University Hospital, Department of General Internal Medicine, Bern, Switzerland

Introduction Estimations of prevalence of T2DM in Switzerland depend on statistical records assembled from fatal causalties, clinically overt disease, reason for hospital admission, outpatient care and are extended recently to laboratory screening in apparently healthy study participants ; the age group looked at might decisively influence the results.
Methods Population-based study with subjectively healthy senior citizens ≥ 60 years. Consecutive participants were recruited between February 2009 and July 2012 as part of the “Senior Labor Study”; subjects with known T2DM were excluded. A total of 1347 healthy subjects were included (604 men, 743 women; age range 60-99 years). In accordance with the current criteria established by international consent, two different blood tests - fasting plasma glucose (FPG) and glycated haemoglobin A1c (HbA1c) - can be used for screening and diagnosis of prediabetes (PreD) and type 2 diabetes mellitus (T2DM). FPG was measured by hexokinase procedure and HbA1c chromatographically using Bio-Rad D 10 HPLC automate. Fasting blood samples were processed immediately for analysis under standardised preanalytical conditions.

Results The crude prevalence of individuals unaware of having PreD, measured by a combination of both tests, was 64.44% (*n*=868), whereas the prevalence of subjects with unknown T2DM was 8.39% (n=113). With the HbA1c criteria, more subjects with unknown PreD and T2DM could be identified than with FPG. Prevalence of PreD as well as of T2DM increases with age, with the curve exhibiting saturation characteristics from 80 years onwards. In the cross-sectional cohort under study, the BMI is gender neutral ($p>0.05$), showing a mean of 25.6 kg/m^2 in men and a mean of 25.4 kg/m^2 in women. The incidence of a HOMA index of >2.5 was low the mean indices for increasing life decennies ≥60 years remaining limited within 2.12 and 2.59.
Conclusions Laboratory-based diagnosis of PreD and T2DM occur frequently among subjectively healthy older Swiss individuals. Introduction of HbA1c as a screening parameter increases the prevalence of T2DM by a factor of 1.6 compared to screening with FPG alone. We need to identify subjects with hyperglycaemia in a timely manner in order to adopt immediate preventive lifestyle modifications and other potential therapeutic interventions for subjects at risk to evolve from healthy to PreD to T2DM based on laboratory screening assays.

FM253 Cardiovascular risk profile and blood pressure control in treated hypertensive patients - an analysis from the Swiss hypertension cohort study

Anja Handschin[1], Andreas Zeller[2], Peter Tschudi[2], Benedict Martina[2], Jörg Leuppi[1], Thomas Dieterle[1]
[1]Medizinische Universitätsklinik, Kantonspital Liestal, Liestal, [2]Institut für Hausarztmedizin (IHAMBB), Universität Basel, Basel, Switzerland

Objective: The relationship between blood pressure (BP) and cardiovascular (CV) morbidity and mortality risk has been demonstrated in a large number of trials. Besides the level of BP, the number of additional CV risk factors and the presence of subclinical and clinical organ damages determine the individual patient risk. However, little data is available on the CV risk profile in primary care populations treated for arterial hypertension. We therefore aimed to evaluate the CV risk category in treated hypertensive patients included into the Swiss Hypertension Cohort Study (HccH) according the guidelines of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC).
Design and methods: HccH is a prospective observational study, which has been initiated in 2005 by the Institute for Primary Care of the University Hospital of Basel. 1005 hypertensive patients were included. Eligible patients are adult men and women (age ≥ 18 years) with arterial hypertension. Inclusion criteria are antihypertensive treatment respectively a mean through sitting office blood pressure (OBPM) ≥140/90 mmHg. Data collection is conducted by general practitioners in Switzerland. Patient characteristics, OBPM, CV risk factors, asymptomatic target organ damage (OD) , diabetes (DM), chronic kidney disease (CKD) and symptomatic CV and renal disease are recorded on an annual basis and CV risk is analyzed according to the 2013 ESH/ESC Guidelines.
Results: CV Risk of 1005 treated hypertensive patients is given in the following table. Data are given as absolute numbers and percentage.

	Normal	High normal	Grade 1	Grade 2	Grade 3
	SBP < 130 or DBP < 85	SBP 130-139 or DBP 85-89	SBP 140-159 or DBP 90-99	SBP 160-179 or DBP 100-109	SBP ≥ 180 or DBP ≥ 110
No other RF	2 (0.2%)	2 (0.2%)	16 (1.6%)	2 (0.2%)	2 (0.2%)
1-2 RF	21 (2.1%)	45 (4.5%)	91 (9.1%)	22 (2.2%)	13 (1.3%)
≥3 RF	65 (6.5%)	78 (7.8%)	132 (13.1%)	40 (4%)	10 (1%)
OD, CKD stage 3, or DM	48 (4.8%)	50 (5%)	87 (8.7%)	31 (3.1%)	6 (0.6%)
Symptomatic CVD, CKD stage ≥ 4	77 (7.7%)	61 (6.1%)	76 (7.6%)	22 (2.2%)	6 (0.6%)
CV Risk Category	Low	Low - Moderate	Moderate	Moderate-High	High	High- Very High	Very High

[CV Risk]

In 78.8% of patients included into HccH, either ≥3 additional CV risk factors, DM, asymptomatic or symptomatic OD were found indicating a high to very high baseline CV risk. An OBPM< 140/90 mmHg was achieved in 44.9% of patients included into HccH.

Discussion: Our data demonstrate that the majority of primary care patients with arterial hypertension included into HccH bear a substantial number of additional CV risk factors, subclinical and/or clinical organ damages, indicating a high to very high CV baseline risk in these patients. Adequate BP control, defined as an OBPM < 140/90 mmHg, is achieved in less than 50% of patients, emphasizing the continuous need for comprehensive CV risk stratification and adequate treatment of arterial hypertension in Switzerland.

FM254 Impact of religiosity on pain processing in chronic pain patients

René Hefti[1], Matthias Laun[2]
[1]Universität Bern, Institut für Spiritualität und Gesundheit, Langenthal, [2]Zentrum für Schmerzmedizin, Nottwil, Switzerland

Background: Several studies have shown the beneficial effect of religiosity in pain patients. Religious coping is seen as a "key" mechanism in promoting adaptation to chronic pain. The present study seeks to further understand how positive and negative religious coping (RCOPE) interact with psychological mechanisms affecting pain control (FESV) and acceptance of pain (CPAQ).

Method: 183 chronic pain patients admitted to the center for pain medicine in Nottwil were surveyed. All patients completed a series of pain questionnaires (CPAQ, DSF, MPSS, FESV, NRS), the Hospital Anxiety and Depression Scale (HADS) as well as two religious measures (RST, Brief RCOPE). The interaction between religious coping, psychological symptoms and coping with pain was assessed using Pearson and Spearman correlations and linear regression.

Results: Correlations revealed significant relationships between positive religious coping and the cognitive as well as behavioral dimensions of coping with pain (FESV, German Pain Coping Questionnaire): Action-Oriented Coping (r = .163*), Cognitive Restructuring (r = .312**), Self-Efficacy (r = .304**), Mental Distraction (r = .206**) and Counter-Activities (r = .149*). Using a linear regression model that included age, sex, anxiety, depression, pain intensity and impairment as confounders confirmed an impact of positive religious coping on cognitive restructuring (R^2 korr = .132, β = .280, p = .000) and self-efficacy (R^2 korr = .271, β = .268, p = .000). An inverse relationship was found between negative religious coping and acceptance of chronic pain (r = -.286, p = .000), suggesting that negative religious coping may be

maladaptive in chronic pain patients.
Conclusions: Present study confirms the association between religiosity and coping with chronic pain. Positive religious coping had a significant positive impact on pain processing, mainly on cognitive restructuring and self-efficacy. Negative religious coping was inversely related to acceptance of chronic pain, and therefore appears to be maladaptive. Both aspects are relevant for the treatment of pain patients.

FM255 Planning and reporting of quality of life outcomes in cancer trials

Stefan Schandelmaier[1], Katrin Conen[2], Erik von Elm[3], Yuki Tomonaga[4], John You[5], Anette Blümle[6], Heiner Bucher[7], Matthias Briel[5,7], Benjamin Kasenda[1,8], on behalf of the DISCO Study Group
[1]Basel Institut for Clinical Epidemiology and Biostatistics, [2]Department of Oncology, University Hospital Basel, Basel, [3]Cochrane Switzerland, Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne, [4]Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zürich, Switzerland, [5]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada, [6]German Cochrane Centre, Medical Center, University of Freiburg, Freiburg, Germany, [7]Institute for Clinical Epidemiology and Biastatistics, University Hospital Basel, Basel, Switzerland, [8]Department of Medical Oncology, Royal Marsden Hospital, London, United Kingdom

Background: Information about the impact of cancer treatments on patients' quality of life (QoL) is of paramount importance to patients and treating oncologists. Several cancer specific and validated QoL instruments exist such as the EORTC QLQ C30 or the FACT. However, randomized clinical trials (RCTs) involving cancer patients often do not report on QoL outcomes. Instead, they typically focus on survival or tumor size as their primary outcome. The reasons for the lack of QoL outcomes are unclear. One reason could be that QoL outcomes are not planned in the study protocol, another reason could be that collected QoL outcome data is subsequently not reported.
Purpose: To investigate whether quality of life (QoL) outcomes were specified in protocols of randomized clinical trials (RCTs) enrolling cancer patients and whether they were subsequently reported.
Methods: Retrospective cohort study of RCT protocols approved by six research ethics committees in Switzerland, Germany, and Canada between 2000 and 2003. We compared protocols to corresponding publications, which were identified through literature searches and investigator surveys.
Results: Of 894 RCTs, 173 enrolled cancer patients. Of the 173 RCTs, 90 (52%) specified QoL outcomes in their protocol, 2 (1%) as primary and 88 (51%) as secondary outcome. Of the 173 RCTs, 35 (20%) reported QOL outcomes in a corresponding publication (4 modified from the protocol), 37 (21%) remained unpublished, and 18 (10%) were published, but failed to report QOL outcomes. Of the 83 (48%) RCTs that failed to specify a QOL outcome in their protocol, none subsequently reported a QoL outcome. Failure to report pre-specified QoL outcomes was not significantly associated with industry sponsorship or trial discontinuation.
Conclusion: About half of cancer RCTs specified QoL outcomes in their protocols. However, only 20% reported any QoL data in associated publications. Highly relevant information is being withheld from patients, oncologists, regulators, and policy makers.

FM256 Case management for emergency department frequent users: a randomized controlled trial

Patrick Bodenmann[1], Venetia-Sofia Velonaki[2], Stéphanie Baggio[3], Katia Iglesias[4], Karine Moschetti[5,6], Ornella Ruggeri[2], Olivier Hugli[7], Bernard Burnand[8], Jean-Blaise Wasserfallen[5,6], Jean-Bernard Daeppen[9]
[1]Vulnerable Population Center, Department of Ambulatory Care and Community Medicine, University of Lausanne, [2]Department of Community Medicine and Public Health, Lausanne University Hospital, Lausanne, [3]Life Course and Social Inequality Research Center, Faculty of Social and Political Sciences, University of Lausanne, [4]Center for the Understanding of

Social Processes, University of Neuchâtel, and Institute of Social and Preventive Medicine, Lausanne University Hospital, [5]Health Technology Assessment Unit, University of Lausanne, [6]Institute of Health Economics and Management, University of Lausanne, [7]Emergency Department, Lausanne University Hospital, [8]Institute of Social and Preventive Medicine, Lausanne University Hospital, [9]Alcohol Treatment Service, Lausanne University Hospital, Lausanne, Switzerland

Background: Emergency department frequent users (EDFUs) account for a disproportionally high number of emergency department (ED) visits, contributing to overcrowding and high health-care costs. At the Lausanne University Hospital, EDFUs account for only 4.4% of ED patients, but 12.1% of all ED visits. Our study tested the hypothesis that an interdisciplinary case-management intervention red.
Methods: In this randomized controlled trial, we allocated adult EDFUs (5 or more visits in the previous 12 months) who visited the ED of the University Hospital of Lausanne, Switzerland between May 2012 and July 2013 either to an intervention (N=125) or a standard emergency care (N=125) group and monitored them for 12 months. Randomization was computer generated and concealed, and patients and research staff were blinded to the allocation. Participants in the intervention group, in addition to standard emergency care, received case management from an interdisciplinary team at baseline, and at 1, 3, and 5 months, in the hospital, in the ambulatory care setting, or at their homes. A generalized, linear, mixed-effects model for count data (Poisson distribution) was applied to compare participants' numbers of visits to the ED during the 12 months (Period 1, P1) preceding recruitment to the numbers of visits during the 12 months monitored (Period 2, P2).
Results: Data were completed for 115 participants in the intervention group and 115 in the control group (N=230; deaths: 10 in each group). Participants' mean age was 44.1 (±17.9), 46% were Swiss, and the majority male (57%) and French speaking (80%); 25% had a low educational level (compulsory education); 43% depended on social welfare; the majority suffered from somatic (69%) or mental (51%) health issues, and 33% presented risk behaviors. The two groups were comparable as regards the number of ED visits during P1. The number of ED visits was lower in P2 compared to P1 for both groups ($b=-0.56$, $p< 0.001$) but the decrease was significantly more important for the intervention group ($b=-0.025$, $p=0.012$).
Conclusion: This study strengthens the evidence that case management leads to a reduction in ED use by EDFUs, through their improved orientation in a universal health coverage system. Given that the total number of ED visits in Switzerland has been steadily growing, our findings should have policy implications for the generalization of such teams on a larger scale, nationally and internationally.

Freie Mitteilungen SGIM: Allgemeine Innere Medizin 6

Communications libres SSMI: Médecine interne générale 6

FM257 Prematurely discontinued randomized trials are frequently labelled "completed" in registries - systematic review

Stefan Schandelmaier[1], Reem Al Turki[1], Kelechi Olu[1], Roy Frei[1], Belinda von Niederhäusern[2], Arnav Agarwal[3], Matthias Briel[1,3]
[1]Basel Institute for Clinical Epidemiology and Biostatistics, [2]Clinical Trial Unit, Department of Clinical Research, University Hospital Basel, Basel, Switzerland, [3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

Background: Trial registries such as clinicaltrials.gov document key information about randomized controlled trials (RCTs). Ideally, RCTs are registered before the start of patient recruitment, and the registry information is updated as the RCT progresses. Registries typically include information about the status of an RCT, i.e. whether it is ongoing, completed, or discontinued. The accuracy of trial status information in registries, however, has never been investigated.
Purpose: To examine whether trial registries label discontinued RCTs accurately as discontinued and provide reasons for RCT discontinuation, and to identify factors associated with inaccurate trial status information.

Methods: Systematic review of published RCTs reported as discontinued and registered. We identified RCTs through systematic searches of MEDLINE and EMBASE (from 2010 to 2014) and through a previous empirical study. Pairs of reviewers extracted independently and in duplicate data from publications and corresponding registries using pre-piloted data extraction forms. We performed multivariable regression to identify risk factors for inaccurate trial status information.
Results: We included 173 discontinued RCTs that were registered in various trial registries, most frequently in clinicaltrials.gov (77%). The discontinued RCTs were typically industry-sponsored, multi-center trials investigating drug therapies. The RCTs were most frequently discontinued due to slow recruitment (62%), futility (19%), or harm (17%).
The registries labelled 45% of the RCTs accurately as discontinued; the remaining RCTs were wrongly labelled as completed (40%), suspended (10%), on-going (5%), or not started yet (1%). If a RCT was accurately labelled as discontinued, registries provided the accurate reason for discontinuation in 33%, an inaccurate reason in 3%, and no reason in 64%.
Accurate registration of trial status significantly improved over time (adjusted odds ratio 1.16 per year; 95% confidence interval, 1.04 - 1.3); trial features such as industry sponsorship, multiple centers, or larger sample size were not significantly associated with accurate trial status information.
Conclusion: Less than half of published discontinued RCTs were accurately labelled as discontinued in registries, and if so, the reason for discontinuation remained mostly unclear. Trial status information in registries should be viewed with caution.

FM258 The interrelationships of birth weight with inflammation and body composition in young adulthood

Thomas Kofler[1,2], Matthias Bossard[1,2,3], Stefanie Aeschbacher[2], Alexandra Tabord[1,2], Javier Ruperti Repilado[1,2], Stephanie van der Lely[1,2], Sebastian Berger[1,2], Martin Risch[4,5], Lorenz Risch[4,6,7], David Conen[1,2]
[1]Department of Medicine, [2]Cardiovascular Research Institute, [3]Cardiology Division, Universitätsspital Basel, Basel, Switzerland, [4]Labormedizinisches Zentrum Dr. Risch, Schaan, Liechtenstein, [5]Division of Laboratory Medicine, Kantonsspital Graubünden, Chur, Switzerland, [6]Division of Clinical Biochemistry, Medical University Innsbruck, Innsbruck, Austria, [7]Private University, Triesen, Liechtenstein

Background: Low birth weight is associated with an increased risk of cardiovascular disease, but the underlying mechanisms are incompletely understood. We hypothesized that differences in body composition and inflammatory biomarker levels may be potential mediators for these inverse relationships.
Methods: Healthy adults aged 25-41 years were enrolled in a prospective population based cohort study in the Principality of Liechtenstein. Main exclusion criteria were diabetes, overt cardiovascular disease or a body mass index >35 kg/m^2. Birth weight was self-reported by the study participants. Bioelectrical impedance analysis was used to determine body composition. Multivariable regression models adjusted for potential confounders were used for statistical analyses. Plasma levels of high-sensitivity C-reactive protein (hs-CRP) were analyzed on a Roche Cobas 6000 analyzer using fresh blood samples. Total white blood cell (WBC) count was determined by using a XE 5000 fluorescence flow cytometry analyzer.
Results: Our sample consisted of 1774 participants (53.4% females) with a median age of 37 years. The median hs-CRP levels and WBC count were 0.9mg/L and 5.3 *10^9/L, respectively. Median and interquartile range of birth weight were 3355g (3050g; 3700g). Main results are shown in the table. In multivariate continuous analyses increase in birth weight was associated with lower hs-CRP levels and WBC count. Additional adjustment for fat mass attenuated these relationships.
In multivariate continuous analyses, the beta coefficient (95% confidence interval) per 100g increase in birth weight was -0.06 (-0.10; -0.03), p< 0.0001 for body fat and -0.002 (-0.03; 0.03), p= 0.91 for muscle mass.
Conclusion: Lower birth weight is associated with inflammation and body fat mass accumulation. Our results suggest that a low birth weight may lead to an increased body fat mass which in turn leads to an increased inflammatory activity and an elevated cardiovascular risk among affected individuals.

Table Multivariable linear regression analyses for the relationship between inflammatory parameters and birth weight

	Continuous*	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
		<3050g	3050-3355g	3355-3700g	3700g	
	(n=1774)	*(n=441)*	*(n=446)*	*(n=442)*	*(n=445)*	***P for trend***
Log-transformed high-sensitive C-reactive protein (mg/L) - Linear regression, β (95% confidence interval)						
model a) †	-0.010 (-0.02; -0.002)**	Ref.	-0.013 (-0.13; 0.10)	-0.02 (-0.14; 0.10)	-0.16 (-0.28; -0.037)	0.01
model b) ‡	-0.008 (-0.02; 0.0003)	Ref.	0.002 (-0.12; 0.12)	0.01 (-0.11; 0.13)	-0.12 (-0.25; 0.001)	0.07
Log-transformed total white blood cell count (*10^9/L) - Linear regression, β (95% confidence interval)						
model a) †	-0.002 (-0.004; -0.0002)**	Ref.	-0.003 (-0.03; 0.02)	-0.02 (-0.05; 0.01)	-0.03 (-0.06; 0.0001)	0.03
model b) ‡	-0.002 (-0.004; 0.0006)	Ref.	0.001 (-0.03; 0.03)	-0.01 (-0.04; 0.02)	-0.02 (-0.05; 0.0109)	0.14

* Transformed variable, per 100g increment in birth weight
** P-value < 0.05
† n=1771; Adjusted for sex, age, BMI, muscle mass, water content, eGFR, systolic blood pressure, LDL, HDL, triglycerides, HbA1c, education level, alcohol consumption, vegetable/fruit consumption, physical activity, smoking (current or past).
‡ n=1771; additionally adjusted for fat mass.

FM259 Swiss Medical Board: what is the impact of its recommendations on routine care in Switzerland?

Klaus Eichler[1], Sascha Hess[1], Marco Riguzzi[1], Ünal Can[2], Urs Brügger[1]
[1]SML, Winterthurer Institut für Gesundheitsökonomie, Zürcher Hochschule für Angewandte Wissenschaften, Winterthur, [2]Stadtspital Triemli, Surgical Clinic, Zurich, Switzerland

Background: Evidence-based recommendations play an important role for medical decision-making, but barriers to adherence are common. In Switzerland, the Swiss Medical Board (SMB) publishes evidence reports that conclude with recommendations. We assessed the impact of two exemplified SMB reports on service provision (2009: Recommendation of conservative treatment as first option for rupture of the anterior cruciate ligament of the knee; 2011: Recommendation against PSA screening for prostate cancer).
Methods: In a multi-method observational study, we assessed quantitative data over time via interrupted times series analyses. We included the quarterly number of PSA-tests from 2005-2013 in 662'874 outpatients and the rates of ACL repair surgery from 1990-2011 in 101'737 patients with knee injury. We collected qualitative data via interviews with 13 physicians and performed literature searches.
Results: Despite some initial change, we did not find a sustained and statistically significant impact of SMB recommendations on the number of PSA screening tests or on the (already declining) rates of surgery for ACL rupture in Switzerland. The controversial public debates in Switzerland about the meaningfulness of SMB recommendations are intermediate results in the domains “dissemination”, “knowledge” and “attitudes”, as reflected in our interviews and retrieved publications.
Conclusions: Impact evaluations remain an important tool for evidence based health services. Our findings do not mean that SMB releases are meaningless. The intensive debate about medical recommendations with influence on knowledge and attitudes is a necessary precondition, that change in the impact domain is possible at all.

FM260 A critical appraisal of the in-hospitality-mortality-rates as quality parameter of a teaching hospital

Petra Ferrari Pedrini[1], Jana Efe[1], Jürg Hans Beer[1,2]
[1]Innere Medizin, Kantonsspital Baden, Baden, [2]Laboratory of Platelet Research, Molecular Cardiology, University of Zürich, Zürich, Switzerland

Introduction: In-hospital mortality rate is used as a quality parameter. Such data often suffer from statistical errors and bias. They are often not correct for case severity and do not account for the palliative care patients. On the other hand, regular discussions in morbidity and mortality conference (MMC) will enhance the quality of a teaching hospital.
Aims of the study and methods: We analysed the in-hospital mortality to distinguish the cases with a true potential for quality improvement from the expected deaths respectively from the pts who died during the palliative pathway. We studied in-hospital deaths from 1/14 - 6/14 and divided them in 5 predefined categories:
1) decision on palliative care was taken at entry.
2) Decision on palliative treatment was taken during hospitalisation.
3) Therapy was limited to the ward. The decision for no admission to the ICU was made with patients and relatives before.
4) Death was expected due to the severity of the disease despite maximum standard of care, mostly in the ICU while timing and measures taken were considered adequate and
5) death occurred rather unexpectedly and deserved detailed analyses, autopsy, and discussion with the attending teams, the admitting physicians and in MMCs in order to detect potentially preventable causes.
Results: We recorded 144 deaths (5.5%) out 2590 hospitalized pts over 6 months.These 144 pts were further analysed: 94.4% were admitted through the ER. The average age was 78 (+/-11), the mean LOS was 10 (+/- 6) days, the average number of active diagnoses was 7 (+/-3). Their CMI was 1.847 (+/- 1.295) compared to the mean total CMI 1.061 .The majority died of advanced tumour stage (31 %) or because of hearth failure (17%). The 6 pts in category 5 were further analysed in detail and prepared for the MMCs of the department.

Category		Deaths	in % of the admissions	in % of the deaths
1	Palliative treatment decision made at admission	39	1.5	27.1
2	Palliative treatment decision made during the hospital stay	49	1.9	34.1
3	A priori limitation of care (no CPR, no IMC, no ICU)	29	1.1	20.1
4	Deaths inevitable/explaned by the severity of the diseases	21	0.8	14.6
5	Deaths with potential for teaching points/improvement	6	0.2	4.1

[Results]

Conclusions:

1. Mortality rates are often misleading and often counterproductive
2. Death in the adequate palliative pathway should be perceived as a quality marker and not as a failure
3. The detailed work-up of the mortality of category 5 in MMC and other quality procedures are strongly suggested. The consecutive implementation of the knowledge is a better quality measure than the crude mortality rates, which may lead to inadequate discharges just before death.
4. The small number of relevant cases of cat 5 is of qualitative value but never suitable for comparable statistics.

Freie Mitteilungen SGIM: Kardiologie / Pneumologie / Gastroenterologie Infektiologie/Immunologie / Rheumatologie

Communications libres SMI:Cardiologie / Pneumologie / Gastroentérologie / Infectiologie / Immunologie / Rhumatologie

FM261 Treatment and outcome of patients with recurrent myocardial infarction

Paul Erne[1], Lea Maurer[2], Osmund Bertel[3], Jean-Christophe Stauffer[4], Dragana Radovanovic[2], AMIS Plus Investigators
[1]Klinik St. Anna, Luzern, [2]AMIS Plus Data Center, Institut für Epidemilogie, BIostatistik und Prävention, Universität Zürich, [3]HerzGefässZentrum, Klinik im Park, Zürich, [4]Service de Cardiologie, Hôpital Cantonal, Fribourg, Switzerland

Background: Although cardiovascular disease is the most frequent reason for hospitalizations in Switzerland, little is known on treatment and outcomes of patients with first or recurrent myocardial infarction (MI). This study aimed to evaluate the baseline characteristics at admission, immediate therapies and outcomes in patients who presented with ST-elevation MI (STEMI) with or without prior MI.
Methods: All STEMI patients enrolled in the AMIS Plus Registry between 2001 and 2014 were included. Outcome was analyzed using logistic multivariate regression. The primary endpoint was in-hospital mortality. In a subgroup of STEMI patients, a 1-year follow-up after discharge was performed.
Results: From the 19,665 STEMI patients, 2845 (14%) had recurrent MI occurring at a median of 40 months (IQR 21, 96 months) after the first one. These patients were older (69.5y vs. 64); P< 0.001), more frequently male (78% vs. 73%; P< 0.001), with hypertension (74% vs. 53%; P< 0.001), dyslipidemia (78% vs 50%; P< 0.001), and more comorbidities (Charlson Comorbidity Index >1 51% vs. 14.2; P< 0.001). Patients with recurrent MI presented 25 minutes earlier than those without a past history of MI and were more frequently in the Killip classes 3/4 (12% vs. 7%; P< 0.001). Unexpectedly, patients with recurrent MI were less likely to receive guideline-recommended drug therapies: aspirin (93% vs. 97%; P< 0.001), P2Y12 inhibitor (76% vs. 83%; P< 0.001), statin (73% vs. 77%; P< 0.001) and to undergo primary percutaneous coronary intervention (77% vs. 87%; P< 0.001). These patients developed more frequently cardiogenic shock (7% vs. 5%; P< 0.001) and reinfarction (2% vs. 1%; P< 0.001) during hospitalization and had higher crude mortality (10% vs. 5%, P< 0.001). Recurrent MI was an independent predictor of in-hospital mortality in STEMI patients (OR 1.41, 95%CI 1.22-1.64; P< 0.001).
The subgroup (n=4486) was followed 1-year after discharge (3893 without and 593 with past history of MI at initial hospitalization). Crude mortality was 2.9% in the first und 6.7% in the second group (OR 1.68, 95%CI 1.14-2.47; P=0.008).
Conclusions: Patients admitted with recurrent MI are high risk patients but they were less likely to receive evidence-based treatment and had worse in-hospital and 1-year outcomes compared to patients with a first MI. Short and long-term management of patients with recurring MI should be improved.

FM262 Which is the best product to use when preparing a colon?

Omar Kherad[1], Sophie Restellini-Kherad[2], Myriam Martel[3], Alan Barkun[3]
[1]Hôpital de La Tour, [2]Hôpitaux Universitaires de Genève, Genève, Switzerland, [3]Mc Gill University Health Center, Montréal, QC, Canada

Background: Adequacy of the colonoscopy bowel preparation is an important predictor of colonoscopy quality.
Aims: To determine a difference in term of effectiveness between different existing colon cleansing products in the setting of a screening program.
Methods: The records of consecutive patients who underwent colonoscopy between April 2013 and April 2014 with information on colonoscopy preparations were retrospectively extracted from our digestive endoscopic institutional database. Descriptive, and inferential statistics were completed, including multivariable logistic regression analysis to determine independent predictors of an adequate colonoscopy preparation (good and excellent).
Results : Overall, 2867 charts were assessed; among them 1130 colonoscopies were performed in a screening setting. In the overall population, mean age was 60.4+13.5 years, 49.9% female, mean ASA score 1.42+0.52. Bowel preparation products used included sodium picosulfate (PICO) (1124, 39.2%), Poly Ethylene Glycol (PEG) (1720, 60%), and adjuvants (368, 12.8%), with split regimens in 119 (4.2%). The cecal intubation rate was 96%, with a mean withdrawal time of 9.4+4.3 mn, resulting in an overall polyp detection rate of 43.8% (45.6% in screening population). Overall, adequate bowel preparation was noted in 84 (90% in screening population). Bowel preparation was worse in patients receiving PICO in comparison to PEG, in both the combined population and a screening setting OR=0.6; (0.5-0.8) and OR=0.5; (0.3-0.7). Regardless of the preparation product, the odds of achieving satisfactory quality cleansing were overall 6.6 times greater for patients receiving a split regimen (OR=6.6; (2.0-21.0)). In multivariable analyses, significant independent clinical factors associated with inadequate bowel preparation in the screening population were use of PICO. In the overall group, additional significant predictors included in-patient status, use of a non-split regimen and the indication of colonoscopy (lowest adequacy of preparations in patients with bleeding and altered bowel habits).
Conclusions: Preparation quality needs to be more consistently included in the colonoscopy report. PEG provides better bowel cleansing efficacy than PICO in a screening setting when considering both day before and split prep regimens. Split dosage regimens increase the quality of colon cleansing across all types of preparations and should be the preferred method of administration.

FM263 Influence of degenerative disorders on the lumbar spine BMD and TBS with age: the Cohort OsteoLaus

Ivan Padlina[1], Didier Hans[2], Bérengère Aubry-Rozier[2], Marie Metzger[2], Olivier Lamy[1]
[1]Service de Médecine Interne, CHUV, [2]Centre des Maladies Osseuses, CHUV, Lausanne, Switzerland

Introduction: After menopause, typically, the values of lumbar spine (LS) BMD and TBS decrease with age. In practice, we are often faced with values of LS BMD "relatively" high for the age, which can lead to erroneous interpretations (reassuring diagnosis, therapeutic gain). Preliminary studies have shown that osteoarthritis (oa) does not influence TBS. The aim of this study was to measure changes in LS BMD and TBS values in women 50 to 80 years, taking into account the impact of fractured vertebrae (VFx) and oa (Voa).
Material and methods: The 1'500 women 50 to 80 years old included in the cohort OsteoLaus (Lausanne, Switzerland) have had LS BMD and TBS, and VFA. 46 exams were not interpretable. All exams were analyzed independently by two experts following the guidelines of the ISCD, excluding in particular VFx (2.7% of participants) and vertebra with > 1 SD difference with the vertebra immediately adjacent (Voa 16.2%).
Results: We included 1'443 women: age 66.7±11.7 years, BMI 25.7±4.4. The correlation between BMD and TBS was low (r2 = 0.16). Participants were divided into six age groups: 50-55 years (n=181 gr1), 55-60 (n=234, gr2), 60-65 (n=353, gr3), 65 -70 (n=319, gr4), 70-75 (n=198, gr5) and 75-80 years (n=158, gr6). BMD was artificially increased from 1.2 to 3.2 % on average according to the gr before excluding VFx and

Voa ($p < 0.001$). TBS didn't change after excluding VFx and Voa (< 0.0% to 0.8%, ns). The correlation (Vfx and Voa excluded) between age and BMD was -0.03, between age and TBS +0.34. BMD (Vfx and Voa excluded) was for the six age gr: 0.953±0.141 g/cm2, 0.916±0.155, 0.909±0.158, 0.917±0.167, 0.918±0.168 and 0.933±0.188, respectively. Loss between 52.5 and 77.5 years was 2.10 %, or 0.09 %/year with a loss of 0.46%/year from 52.5 to 62.5 years, followed by a gain of 0.18 %/year between 62.5 and 77.5 years. The change in BMD between two consecutive age gr was significant only between gr1 and gr2 ($p < 0.02$). TBS (Vfx and Voa excluded) was for the six age gr: 1.357±0.093, 1.317±0.099, 1.289±0.092, 1.269±0.099, 1.253±0.101 and 1.235±0.105, respectively.
Conclusion: This study confirms the low correlation between LS TBS and BMD. It shows a double interest in TBS:
1) on average, TBS is not affected by fractures or oa disorders,
2) while BMD increases after 65 years (moderate degenerative disorders cannot be excluded from the analysis), TBS continues to decline. For the LS evaluation, TBS should play a leading.

FM264 Alendronate improves bone material level properties in paired human transiliac bone biopsy specimens

Patrick Ammann, René Rizzoli
Service des Maladies Osseuses, Genève, Switzerland

Bone strength, hence fracture risk, is dependent on bone geometry, microstructure and bone material level properties. Alendronate treatment maintains bone mass and prevents further microarchitecture deterioration. Indeed only an improvement of bone material level properties, could explain the decrease in fracture risk. We investigated the effects of alendronate treatment on bone material level properties and bone microarchitecture of transiliac bone biopsies from postmenopausal osteoporotic patients. In a longitudinal study, 76 paired biopsies in 38 patients were obtained at baseline and after 6 or 12 months of treatment with alendronate 70 mg once weekly. Elastic modulus, hardness and working energy were blindly analyzed by nanoindentation at the level of the interstitial and haversian bone of the cortex and of trabecular nodes and remodeling units under humid conditions. Parameters of microarchitecture were evaluated by microCT (Scanco Medical). Values are mean±SEM, significance of differences are evaluated by Student's unpaired t-test, **p< 0.01,
***p< 0.001. Bone microarchitecture was not influenced by alendronate treatment. At the level of the interstitial cortical bone, changes in bone material level properties were observed; modulus was at base line 13.31±0.18 gPa and after 6 months of treatment 14.46±0.20 *** and hardness 3189±37pJ at base line and 3372±43 ** after 6 months of treatment. In summary, changes in bone material level properties were observed at the level of the interstitial cortical bone at the two time points and only by 12 months in haversian bone, but not at the level of the trabecular bone. Thus a prevention of deterioration cannot be excluded at the level of the trabecular bone since a progressive alteration was observed after the menopause. The positive effect on bone material level properties of alendronate could be partially explained by the known increase of mean degree of mineralization and could contribute to the known improvement of bone strength since no modification of bone mass was observed. Interestingly this study indicates that bone material level properties which represents a target for anti-osteoporotic treatment, could be selectively improved by alendronate.

Freie Mitteilungen SGIM: Allgemeine Innere Medizin 2

Communications libres SSMI: Médecine interne générale 2

FM265 Hospital potentially avoidable readmission in general internal medicine: elaboration of a predictive score

Anne-Laure Blanc[1,2,3], Thierry Fumeaux[2], Jérôme Stirnemann[1], Marc Carpentier[1], Aimad Ourahmoune[1], Jules Desmeules[1], Pierre Chopard[1], Arnaud Perrier[1], Nicolas Schaad[4], Pascal Bonnabry[1]
[1]Hôpitaux Universitaires de Genève, Genève, [2]Groupement hospitalier de l'ouest-lémanique (GHOL), Nyon, [3]Ecole de pharmacie Genève-Lausanne (EPGL), Université de Genève, Université de Lausanne, Genève, [4]Pharmacie Interhospitalière de la Côte (PIC), Morges, Switzerland

Background: Patients at risk of readmission should be identified early during hospital stay, in order to benefit from specific interventions. The aim of this study was to characterize patients readmitted in two Swiss hospitals, with a specific focus on medication profile, in order to create a predictive tool of hospital potentially avoidable readmissions.
Method: This retrospective study included all patients identified by SQLape algorithm as readmitted within 30 days in 2011 in general medicine wards in HUG and GHOL. Control patients, not identified by SQlape as readmitted, were matched on age and sex. Factors associated with potentially preventable readmission were identified with a multivariate logistic regression. Variables of interest were demographic data, diagnoses, lab results and medications at hospital discharge. A predictive score was developed using a regression coefficient-based scoring method.
Results: 982 patients (275 readmitted and 707 controls, mean age (SD) 68.9 (16.2) years, 60% male) were included. The variables of interest found to be significantly associated with potentially avoidable readmissions in the multivariate logistic regression [adjusted OR (95CI)] were: COPD [1.60(1.02-2,48)], heart failure [2.02(1.41-2.91)], length of stay > 14 days [2.04(1.38-2.99)], malignancy [1.46(1.02-2.06)], myocardial infarction or ischemic cardiopathy [1.72(1.17-2.51)], previous admission within 6 months [2.21(1.63-2.99)], hyperkaliemia [2.47(1.26-4.94)] and RAA drugs [0.50(0.35-0.71)]. Drug classes, numbers of drugs prescribed or drug-drug interactions at hospital discharge were not associated with an increased risk of hospital potentially avoidable readmissions in this study.
Based on these results, the HIPPOCCRAS score was developed (characteristics - points):

H	Heart failure	7
I	Myocardial Infarction or Ischemic cardiopathy	5
P	Previous admission within six months	8
P	Potassium >5.5 mmol/L	9
O	Oncological comorbidities	4
C	COPD	5
C	Cognitive comorbidities*	5
R	RAA drugs	-7
A	Anemia*	2
S	Length of Stay > 14 days	7

[Table 1: HIPPOCCRAS score]
**non significative but predictive covariate
The calibration and discriminatory power of this score were fair with an area under the ROC curve (C-statistic) of 0.714.
Conclusion: This retrospective study identified several factors significantly associated with potentially avoidable readmissions and routinely available during hospital stay. Based on these results, a predictive score has been developed and a retrospective external validation will be performed in order to confirm these results.

FM266 Diagnostic recalibration of myocardial infarction 10 year risk calculators using carotid atherosclerosis imaging in two large cohorts from Germany and Switzerland: a new tool for rapid adjustment of coronary risk by regions

Michel Romanens[1], Franz Ackermann[1], Thomas Szucs[2], Isabella Sudano[3], Ansgar Adams[4]
[1]Vascular Risk Foundation (Varifo), Olten, [2]European Centre of Pharmaceutical Medicine (ECPM), Basel, [3]University Heart Center Cardiology, University Hospital Zürich, Zürich, Switzerland, [4]B.A.D Gesundheitsvorsorge und Sicherheitstechnik GmbH, Bonn, Germany

Background: Risk calculators use similar risk factors and should therefore produce similar accuracies. Sensitivity to detect high coronary risk may be too low, evidencing the need for recalibration.
Methods: Total carotid plaque area TPA ≥80 mm^2 (TPA80) defines high coronary risk (Arterioscler Thromb Vasc Biol. 2014;34:226-230). ROC and sensitivity / specificity (SENS/SPEC) analysis for detection of TPA80 for ASCVD, FRAMINGHAM, ESC, ESC-HDL, PROCAM, and AGLA2014 was determined. SPEC 85% was chosen in order to obtain a SENSc of at least 30%. 10 year risk at SPEC85% was determined (Cut value) and high risk definition (5% for ESC, 20% for the others) was divided by the cut value thus obtaining the recalibration factor.
Results: The baseline characteristics of CH and DE was: N=1601 and 2633, mean age 55±7 and 49±7 years respectively; and subjects with TPA ≥80 mm^2 were found in 18% and 18%, respectively.

	ASCVD	FRAM	ESC	ESC HDL	PROCAM	AGLA 2014
Average risk CH (%)	6.9	9.0	1.3	1.0	6.0	4.2
Average risk DE (%)	4.1	6.4	0.7	0.6	5.2	
ROC CH (95%CI)	0.728 - 0.771	0.726 - 0.769	0.716 - 0.760	0.730 - 0.773	0.700 - 0.744	0.700 - 0.744
ROC DE (95%CI)	0.807 - 0.836	0.801 - 0.831	0.800 - 0.830	0.803 - 0.833	0.798 - 0.828	
[Risk according to various algorithms]	ASCVD	FRAM	ESC	ESC HDL	PROCAM	AGLA 2014
SENS CH (95%CI)	5.6 - 12.3	14.1 - 23.2	2.1 - 7.0	0.7 - 4.4	8.4 - 16.1	
SPEC CH (95%CI)	96.7 - 98.4	94.0 - 96.3	97.9 - 99.2	98.7 - 99.7	95.2 - 97.3	
SENS DE (95%CI)	0.5 - 2.7	6.5 - 11.8	0.6 - 3.0	0.05 - 1.5	14.1 - 21.1	
SPEC DE (95%CI)	99.7 - 100.0	98.1 - 99.1	99.7 - 100.0	99.7 - 100.0	97.6 - 98.8	
SENSc CH (95%CI)	36.7 - 48.2	34.0 - 45.5	35.7 - 47.2	36.3 - 47.9	31.8 - 43.1	
SENSc DE (95%CI)	53.9 - 63.0	53.5 - 62.5	51.1 - 60.3	53.5 - 62.5	51.1 - 60.3	
Cut Value (%)	11.2	13.81	2.05	2.1	9.6	
Recal Factor CH	1.81	1.45	2.44	2.40	2.08	2.97
Recal Factor DE	2.28	2.20	4.67	5.75	2.71	

[Diagnostic accuracy of various algorithms]

Conclusion: TPA ≥80 had a prevalence of 18% in CH and DE. All risk calculators underestimated this

coronary risk, evidencing the need for recalibration by a factor of 1.45 to 5.75. Our recalibration model allows for a rapid adjustment of coronary risk factors at the regional level and helps to correct for the complete lack of contemporary data to calibrate risk calculators.

FM267 Nursing home residents at the emergency department: a 6-year analysis in a Swiss academic hospital

Pierre-Nicolas Carron[1], Cédric Mabire[2], Bertrand Yersin[1], Christophe Büla[3]
[1]Emergency Department, Centre Hospitalier Universitaire Vaudois, [2]University of Health Sciences (HESAV), [3]Service of Geriatric Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Introduction: The increasing number of oldest-old persons induces an increase in emergency department (ED) visits by these elderly patients. At the same time, a disproportionate increase in ED visits by nursing home (NH) residents is observed. This trend implies a major challenge for the ED in the context of scarce resources and limited specific skills of emergency professionals in caring for this population. This study sought to investigate emergency department (ED) visits by nursing home (NH) residents in a Swiss academic hospital.

Methods: A retrospective analysis was performed of all ED visits by NH residents aged 65 years and over (65+ y) that occurred between 2005 and 2010 at the Lausanne University Hospital in Lausanne, a Swiss urban area. Socio-demographic data, mode of transfer to ED, triage severity rating, main reason for ED visit, ED and hospital length of stay, as well as discharge dispositions, and readmission at 30 and 90-day were collected.
Results: Annual ED visits by NH residents increased by 50.1 % (from 465 to 698) over the study period, accounting for 1.5% to 1.9% of all ED visits from 2005 to 2010, respectively. Over the same period, yearly rates of ED visits increased steadily from 18.8 to 27.5 per 100 NH residents. Top-five reasons for ED visits were trauma, respiratory, cardiovascular, digestive, and neurological problems and remained the same over the study period. About half (51.9%) visits were for urgent situations. Less than 2% of the residents died during their ED stay and almost 60% were admitted to the hospital.
Conclusion: ED use by NH residents increased disproportionately over the study period, likely reflecting the combined effect of changes in residents and caregivers' expectations, NH staff care delivery, as well as possible correction of prior ED underuse. These results highlight the need to both improve ED process of care to these frail patients, as well as to identify and implement potential interventions to possibly address these increased needs at the NH level to prevent unnecessary ED transfer.

FM268 "Less is more": unexpected high diagnostic inpatient blood loss and ways to reduce it - "The VAMP-study"

Mary-Monica Papaux[1], Hans-Ruedi Schmid[1], Livia Hajbok[1], Silvia Brims Koponen[2], Hans-Jürg Beer[1,3]
[1]Innere Medizin, [2]Innere Medizin, Intensivstation, Kantonsspital Baden, Dättwil, [3]Universitätsspital Zürich, Zürich, Switzerland

Introduction: Blood samples in patients (pts) for diagnostic testing may reach unexpected high volumes and could lead to iron deficiency or anaemia. Major bleeding, defined as a drop of - 2 g % haemoglobin, is associated with more frequent major adverse cardiac events. This study aims to quantify the blood volumes lost and to define strategies to reduce them as suggested earlier (Levi M, JTH, 2014).
Methods: Three groups of patients were evaluated between 1/2013 - 1/2015. A) Medical and B) surgical ICU-patients with a case mix index (CMI) >21 were analysed as well as C) a series of randomly selected medical inpatients without ICU-treatment (Table). The amount of blood (ml) was determined per day as well as over the total hospital stay. The haemoglobin was monitored at the beginning and at the end of the

hospitalization and the number of blood transfusions given was determined.
Results: The maximum of blood drawn during a hospitalization period was as high as 3.5 l. Mean values were in group A) 1749 ml (809 - 3475 ml), in B) 2261 ml (1667 - 2620 ml) and in C) 85 ml (48 - 132 ml). The average length of stay was 50 days (14 - 77) in group A), 120 days (64 - 177) in group B) and 16 days (9 - 23) in group C). This represents a daily diagnostic blood loss of 37 ml, 20 ml and 5 ml, respectively. The haemoglobin dropped from 11.6 g % to 9.5 g % in A), from 11.5 g % to 9.9 g % in B) and from 13.1 g % to 11.4 g % in C). On the other hand, patients received an average number of blood transfusion units of 5.3, 16.3 and 0 respectively (Table).
Conclusions:
a) The results show that diagnostic blood sampling may be extensive, particularly in ICU-patients. This will often cause and enhance anaemia by more than 2g %. The later is potentially associated with major adverse cardiac events and with deterioration of other comorbidities.
b) More than half of the blood samples and approximately 1700 l/year will be discarded in a 380 bed Teaching Hospital.
c) 50% of the diagnostic blood volume drawn might be reduced by the introduction of simple measures such the use of small blood sampling tubes.

	Gender	Age (mean ± SD)	CMI	Hb at admission	Hb at discharge	Units transfused	Volume drawn per day (ml)	Total volume drawn per patient (ml)
medical ICU (7 pts)	3F/ 4M	63 ± 14.9	21.1	11.6 ± 2.3	9.5 ± 1.5	5.3	37	1749
surgical ICU (4 pts)	1F/3M	60 ± 9.8	21.1	11.5 ± 3.5	9.9 ± 0.5	16.3	20	2261
medical inpatients without ICU (8 pts)	2F/6M	80 ± 7.2	1.6	13.1 ± 1.9	11.4 ± 2.1	0	5	85

[Table]

Freie Mitteilungen SGIM: Allgemeine Innere Medizin 3

Communications libres SSMI: Médecine interne générale 3

FM269 May increasing incidence of breast cancer be related to overdiagnosis? A population-based study

Christina Bruder[1], Isabelle Konzelmann[2], Valérie Gloor[3], Nicolas Rodondi[4], Jean-Luc Bulliard[1], Arnaud Chiolero[1]
[1]IUMSP, Lausanne University Hospital, Lausanne, [2]Registre valaisan des tumeurs, [3]Observatoire valaisan de la santé, Sion, [4]Department of General Internal Medicine, Inselspital, Bern University Hospital, Berne, Switzerland

Background: Breast cancer is the first cause of cancer in women in Switzerland. While breast cancer mortality has sharply decreased in the two last decades in Switzerland, the incidence of breast cancer has increased during the same period. Various reasons for this increase have been hypothesized, such as the increase in the prevalence of obesity, the use of postmenauposal hormone replacement therapy, or a later age for having a first child. Overdiagnosis secondary to screening and any other forms of early detection procedures could be also involved. Analyses of breast cancer by stage can help evaluate if overdiagnosis

could have contributed to the increase in the incidence of breast cancer.
Methods: We used data from the Valais cancer registry at the Observatoire valaisan de la santé (www.ovs.ch). This population based registry collects data on all new (incident) cases of cancer diagnosed in women living in one canton of Switzerland, Valais. Cancers are coded according to the International Classification of Diseases for Oncology (ICD-O-3) and the stages are coded according to the TNM classification. Information on breast cancer stage (in situ: 0; invasive: I, II, III, IV) was available for all cases recorded between 1993 and 2011 (N=4246). Standardized rates of breast cancer were computed (direct standardization on European population).
Results: The standardized incidence of breast cancer has increased between 1993-1996 and 2007-2011, from 123/100'000 to 139/100'000 inhabitants (+16/100'000). There was a large increase in the incidence of early stages (0/I) and a small decrease of intermediate (II/III) and late (IV) stages. The absolute increase in the incidence of early stages cancers (+25/100´000) was larger than the total absolute decrease in the incidence of intermediate and late stages cancers (-7/100´000).
Conclusion: Between 1993 and 2011, the reduction in intermediate and late stages of breast cancer in this region of Switzerland was accompanied by a substantial - and larger in absolute term - increase in the incidence of early stage. Overdiagnosis could have contributed to such imbalance in stage-specific trends. Further studies are needed to estimate the effect of screening and any other forms of early detection procedure on these trends.

FM270 Usability of the electronic medical record in a hospital daily usage: feedback from the doctors

Antoine Garnier, Mariangela Gagliano, Aude Giger
Internal Medicine Department, University Hospital of Lausanne, Lausanne, Switzerland

Background: Because of the increase of information quantity, complexity, and turnover, the electronic medical record (EMR) has become the major tool for daily practice. Interns declare keeping eyes on it for more than half of the day. Current EMR was introduced in 2010 in our university internal medicine department. Because of regular complains about usability, we wanted to collect a comprehensive feedback from the end-users.
Method: We asked all physicians working in our department for the 6 last months to complete an online survey. Assignment was
1) to assess significance of 14 factors defining usability;
2) to rank 9 information technology (IT) systems according to usability;
3) to assess the usability of 47 tasks done with EMR on a numeric scale (1=not usable, 6=perfectly usable). Tasks were sorted in coherent groups (*table 1*). Beside, physicians might add free text comments. Results were shared with IT department and executive management.
Results: February 2014, we sent 126 emails. After two general and one individualized reminders, we received 113 responses (90%). 9 empty or partially empty surveys were excluded. We received 207 free text comments. Most significant factors defining usability were easiness to use (88.5% of physicians), minimal numbers of steps to complete one task (73.5%), and easiness to retrieve information (69.9%). Compared with other IT systems, EMR was ranked in last position (average rank: 8.3th over 9). Physicians evaluated the EMR overall usability at 2.9 over 6 (standard deviation: 0.6). On average, « looking for results » group was best assessed (3.6). Worst assessed groups were « having overview » (2.5) and « making plan » (2.3). Most frequent comments were: too many mouse clicks, lack of synthetic view, lack of project view, and difficulty to retrieve information.
Conclusion: High responses rate and high number of comments demonstrate the importance of EMR for physicians and their significant involvement. Poor evaluation of usability shows a progression margin and part of improvements must be assumed by IT. However, physicians have to rethink the day organization and tasks delegation according to the current evolution. They should stay involved in the development process of EMR.

Tasks	Average	SD
Having the overview	**2.5**	**0.8**
Get overview of a patient	2.5	1.0
Quickly identify critical information	2.3	1.0
Perceive the chronology of hospitalization	2.4	1.2
Understand recent developments in the patient	2.6	1.1
Look for vital parameters	2.6	1.3
View the paramedical information	2.8	1.1
Writing an admission protocol	**3.0**	**0.8**
Fill the admission protocol in emergency department	3.5	1.2
Fill the admission protocol in medicine ward	3.2	1.2
List the problems	3.3	1.0
Make a differential diagnosis	2.7	1.2
Document specific aspects of the patient (allergy)	2.5	1.2
Updating the record	**3.2**	**0.8**
Write medical notes	4.0	1.3
Update existing documentation	3.1	1.1
Write a transmission protocol	2.6	1.1
Prescribe radiological exams	3.0	1.2
Looking for archives	**2.8**	**0.8**
Look for a discharge letter	3.4	1.2
Consult archived documents	2.5	1.3
Learn about the medical history	2.3	1.2
Learn about the stays history	2.6	1.2
Consult a patient's record in another department	3.2	1.2
Viewing results	**3.6**	**1.0**
Consult the laboratory results	4.0	1.3
Read a radiological report	3.6	1.3
Read a microbiology result	3.6	1.4
Read a cytopathological result	3.1	1.4
Read a consultation	3.5	1.2
Doing lists	**2.6**	**0.8**
Get overview of a care unit	2.8	1.2
Build a personal list of patients	3.3	1.3
Build a specific list of patient	2.8	1.2
Identifing bed placed patients	2.1	1.1
Print medical documentation	1.8	1.0
Administrative data	**2.9**	**0.8**
Look up a patient record	3.3	1.3
Change the administrative data of a patient	2.4	1.1
Locate the patient geographically	3.2	1.3
Look at the administrative data of a patient	3.0	1.1
Search information on relatives of a patient	2.5	1.3
Identify physicians in charge of the patient	3.3	1.3
Identify involved external doctors	2.5	1.2
Writing reports	**3.4**	**0.9**
Write a consultation report for another service	3.7	1.2
Write a certificate	3.0	1.3
Write a discharge report	3.1	1.2
Correct and sign medical reports	3.5	1.3
Get the overview of the reports to be signed	3.7	1.4
Making plans	**2.3**	**0.9**
Define the patient's project	2.5	1.0
Learn about the patient's project	2.4	1.0
Estimate and document the likely length of stay	2.1	0.9
Learn about the likely length of stay	2.1	0.9
Report an interview with the family of a patient	2.3	1.1
Global average	**2.9**	**0.6**

Table 1. Assessment of the usability of EMR through 47 tasks. Question was "How do you assess the usability of EMR for the following tasks, on a scale from 1, not usable to 6, perfectly usable." Listed tasks have been selected based on senior chiefs resident expertise. SD : standard deviation.

[Assessment of the usability of EMR through 47 task]

FM271 Subclinical thyroid dysfunction and frailty among older men

Vanessa Virgini[1], Nicolas Rodondi[2], Peggy Cawthon[3], Stephanie Harrison[3], Andrew Hoffman[4], Eric Orwoll[5], Kristine Ensrud[6], Douglas Bauer[7], MrOS Study Group
[1]Universitätsspital Zürich, Zürich, [2]Inselspital, Bern University Hospital, Bern, Switzerland, [3]California Pacific Medical Center Research Institute, San Francisco, [4]Stanford University Medical School, Palo Alto, CA, [5]Oregon Health & Science University, Portland, OR, [6]University of Minnesota, Minneapolis, MN, [7]University of California San Francisco, San Francisco, CA, United States

Introduction: Both subclinical thyroid dysfunction and frailty are frequent among elderly, but data on the relationship between these two conditions are conflicting. Our objective was to assess the cross-sectional and prospective associations between subclinical thyroid dysfunction and frailty, and its five sub-domains.
Methods, setting and design: The Osteoporotic Fractures in Men Study (MrOS), a prospective cohort study.
Participants: Men over 65 years (n = 1455) classified into three thyroid states groups: subclinical hyperthyroidism (TSH < 0.55 mIU/L, normal FT4 levels, N=26, 1.8%), subclinical hypothyroidism (TSH > 4.78 mIU/L, normal free T4 levels, N=102, 7.0%) and euthyroidism (TSH 0.55-4.78 mIU/L, N=1327, 91.2%).
Main outcome measures: Frailty was defined using a slightly modified Cardiovascular Health Study Index: men with 3 or more criteria (shrinking, weakness, slowness, exhaustion and low activity) were considered as frail, men with 1-2 criteria as intermediately frail and men with no criteria as robust. We assessed the relationship between thyroid function and three categories of frailty status (robust/intermediate/frail) at baseline and the same classification plus mortality after a 5-year follow-up.
Results: At baseline, compared to euthyroid participants, men with subclinical hyperthyroidism were more likely to be frail (adjusted odds ratio (OR)=2.48, CI: 1.15, 5.34), particularly among men < 74 years at baseline (OR for frailty=3.63, CI: 1.21, 10.88) who also had an increased likelihood of weakness (OR=3.41, CI: 1.03, 11.30). Men with subclinical hypothyroidism were not more likely to be frail (OR=0.94, CI: 0.08, 0.77). After 5 years of follow-up, baseline subclinical hypothyroidism and hyperthyroidism were not consistently associated with overall frailty status or frailty components.
Conclusion: Among well-functioning community-dwelling men, subclinical hyperthyroidism, but not subclinical hypothyroidism, is associated with increased odds of prevalent but not incident frailty.

FM272 Feedback based on videotaped consultations or immediately after direct observation: which is more effective?

Noelle Junod Perron[1,2], Martine Louis-Simonet[1], Bernard Cerutti[2], Eva Pfarrwaller[2], Johanna Sommer[2], Mathieu Nendaz[1,2]
[1]Geneva University Hospitals, [2]Geneva Faculty of Medicine, Geneva, Switzerland

Introduction: Geneva medical school offers the opportunity to medical students to practice clinical skills with simulated patients during formative sessions in order to prepare them for clerkships. These sessions, are given in two formats:
1) direct observation of a consultation followed by verbal feedback (direct feedback) and
2) postponed observation of the videotaped consultation by both student and tutor and verbal feedback within the same session (video-based feedback).
The aim of the study was to evaluate to which extent content and process of feedback differed between both formats.
Methods: During 2013, all 2nd and 3rd year medical students and tutors (clinical supervisors) involved in formative sessions were asked to take part into the study. A sample of audiotaped feedback sessions involving tutors who gave feedback in both formats was analysed (content and process of the feedback) using a 30 item feedback scale (Likert scale 0-5).
Results: 48 audiotaped feedback sessions involving 12 tutors were analysed (2 direct and 2 video-based sessions per tutor). When adjusted to the length of feedback, there were significant differences in terms of content and process between both formats: the number of communication skills and clinical reasoning items addressed was higher in the video-based format (respectively 11.29 vs 7.71 $p < 0.003$ and 3.71 vs 2.04 $p < 0.003$). Tutors involved more actively students during the video-based sessions than during direct feedback

sessions (self-assessment: 4.00 vs 3.17, p 0.003; active problem solving 3.92 vs 3.42, p 0.004; balanced verbal interaction 4.08 vs 3.54, p 0.003).
Conclusion: Video-based feedback seems of higher quality than direct feedback regarding the content addressed and the processes used to actively involve the students. Providing residents opportunities to receive feedback based on videotaped encounters may be more effective than offering direct feedback during clinical practice, as occurs for example during mini CEX sessions.

Freie Mitteilungen SGIM: Allgemeine Innere Medizin 4

Communications libres SSMI: Médecine interne générale 4

FM273 Educational level, anticoagulation quality, and clinical outcomes in patients with acute venous thromboembolism

Eveline Hofmann[1], Andreas Limacher[2], Marie Méan[1,3], Tobias Tritschler[1], Nicolas Rodondi[1], Drahomir Aujesky[1]
[1]Department of General Internal Medicine, Bern University Hospital, [2]Clinical Trials Unit, University of Bern, Bern, [3]Department of General internal Medicine, Lausanne University Hospital, Lausanne, Switzerland

Background: Previous studies have demonstrated an association between a lower educational level and an increased risk for venous thromboembolism (VTE). However, whether the educational level is associated with anticoagulation quality and clinical outcomes in patients with acute VTE is unknown.
Methods: We studied 817 patients aged ≥65 years with acute VTE from a Swiss prospective multicenter cohort study between September 2009 and December 2013. We defined three educational levels:
1) less than high school (≤9 years of education),
2) high school, or
3) post-secondary (diploma from a university or an equivalent institution).
The primary outcome was the quality of anticoagulation, expressed as the percentage of time in therapeutic INR range (2.0-3.0). Secondary outcomes were the time to a first fatal or non-fatal recurrent VTE, and the time to a first fatal or non-fatal major bleeding. We examined the association between educational level and outcomes using linear and competing risk regression, adjusting for patient baseline characteristics and treatments, including periods of anticoagulation as a time-varying covariate.
Results: Overall, 56% of patients had a less than high school, 25% a high school, and 19% a post-secondary educational level. The median time spent in the therapeutic INR range was 64% for patients with less than high school, 68% for patients with high school, and 65% for patients with a post-secondary educational level (*P*=0.27). After adjustment, we found no association between educational level and time in the therapeutic INR range. Furthermore, there was no association between educational level and recurrent VTE or major bleeding (Table).
Conclusions: In our prospective multicenter cohort, we did not find an association between educational level and anticoagulation quality or medical outcomes in patients with acute VTE.

Educational level	Adjusted sub-hazard ratio (95% confidence interval)
Recurrent venous thromboembolism	
Less than high school	-
High school	0.97 (0.58-1.65)
Post-secondary	1.16 (0.69-1.96)
Major bleeding	
Less than high school	-
High school	1.13 (0.70-1.82)
Post-secondary	1.40 (0.82-2.38)

[Association between education and medical outcome]

FM274 Is subclinical thyroid dysfunction associated with recurrent venous thromboembolism? A prospective cohort of elderly patients

Daniel Segna[1], Marie Méan Pascual[1,2], Andreas Limacher[3], Christine Baumgartner[1], Manuel R. Blum[1], Jürg Hans Beer[4], Nils Kucher[5], Christian M. Matter[6], Marc Righini[7], Beat Frauchiger[8], Jacques Cornuz[9], Markus Aschwanden[10], Martin Banyai[11], Bernhard Lämmle[12], Joseph Osterwalder[13], Marc Husmann[14], Michael Egloff[15], Daniel Staub[10], Anne Angelillo-Scherrer[12], Drahomir Aujesky[1], Nicolas Rodondi[1]

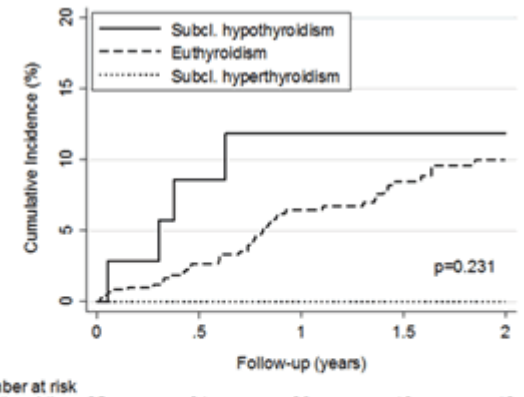
[1]Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, [2]Department of General Internal Medicine, University Hospital of Lausanne, Lausanne, [3]Clinical Trial Unit, Department of Clinical Research, and Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, [4]Department of Internal Medicine, Cantonal Hospital of Baden, Baden, [5]Division of Angiology, Inselspital, Bern University Hospital, Bern, [6]Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, [7]Division of Angiology and Hemostasis, Geneva University Hospitals, Geneva, [8]Department of Internal Medicine, Cantonal Hospital of Frauenfeld, Frauenfeld, [9]Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Lausanne, [10]Division of Angiology, University Hospital Basel, Basel, [11]Division of Angiology, Cantonal Hospital of Lucerne, Lucerne, [12]Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, Bern, [13]Emergency Department, Cantonal Hospital of St Gallen, St. Gallen, [14]Division of Angiology, University Hospital Zurich, Zurich, [15]Division of Endocrinology and Diabetes, Geneva University Hospitals, Geneva, Switzerland

Background: Venous thromboembolism (VTE) is common in the elderly and its incidence increases with age. Current data suggest that subclinical hypothyroidism (SHypo) may be associated with a hypercoagulable state, a higher prevalence of VTE and an increased risk for thromboembolic events in the arterial bed. Prospective data on the relationship between thyroid function and recurrent VTE (rVTE) are lacking.

Methods: Thyroid function was measured in 561 patients aged ≥65 years with acute VTE in a prospective multicenter cohort study in Switzerland. Since thyroid hormones may be influenced by acute thrombosis, these parameters were determined in a blood sample 1 year after the index VTE. We defined SHypo as thyroid stimulating hormone level (TSH) between 4.50 and 19.99 mIU/l, and subclinical hyperthyroidism (SHyper) as TSH< 0.45 mIU/l, both with normal free thyroxine levels. Outcomes were incidence of rVTE and overall mortality during follow-up starting after the 1-year blood sampling. We examined the association between thyroid function and rVTE as well as overall mortality, using competing risk regression with adjustment for patient baseline characteristics (age, sex, risk factors for rVTE: i.e. prior VTE, cancer, idiopathic VTE) and periods of anticoagulation as a time-varying covariate.

Results: Of 561 patients, 35 (6%) had SHypo and 26 (5%) SHyper. After a mean follow-up of 20.8 months (standard deviation: 9.1 months), 52 (9%) patients developed a rVTE and 56 (10%) died. The incidence of rVTE was 7.2 (95% confidence interval: 2.7-19.2) per 100 patient-years in SHypo and 5.9 (4.4-7.8) in euthyroid patients. Multivariate analyses indicate a pattern of increased risk for rVTE in SHypo compared to euthyroids (hazard ratio [HR] 1.50, 0.52 - 4.34, p=0.46) and in TSH as a continuous variable (HR 1.18 per log-unit increase, 0.87-1.60. p=0.28), that both did not reach statistical significance. We found no association, neither between SHypo (HR 0.99, 0.30-3.29, p=0.98) nor TSH (HR 0.88 per log-unit increase, 0.66-1.18, p=0.41) and mortality. Patients with SHyper did neither develop any rVTE nor had an increased mortality risk (HR 0.80, 0.23-2.81. p=0.73).

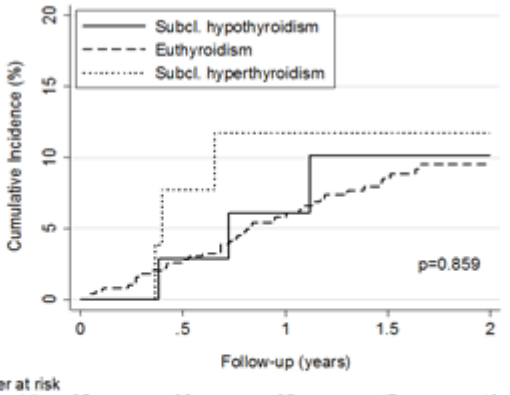
Conclusion: In this prospective cohort study of elderly patients with VTE, SHypo and SHyper were neither associated with rVTE nor mortality. In contrast to the increased risk of arterial cardiovascular diseases described in literature, SHypo does not appear to be significantly associated with recurrent VTE.



Number at risk					
Subcl. hypothyroidism	35	31	23	16	12
Euthyroidism	500	458	357	261	155
Subcl. hyperthyroidism	26	23	21	17	11

Legend:
subcl.: subclinical
rVTE: recurrent venous thromboembolism

[Cumulative incidence of rVTE by thyroid state]



Number at risk					
Subcl. hypothyroidism	35	33	25	17	13
Euthyroidism	500	469	380	282	171
Subcl. hyperthyroidism	26	23	21	17	11

Legend:
subcl.: subclinical
rVTE: recurrent venous thromboembolism

[Cumulative incidence of mortality by thyroid state]

FM275 Is it realistic to face chronic patient congestion without increasing capacity?

Antoine Garnier[1], Valérie Chavez-Demoulin[2], Ari-Pekka Hameri[2], Tapio Niemi[2], Gérard Waeber[1], Jean-Blaise Wasserfallen[3]
[1]Internal Medicine Department, University Hospital of Lausanne, [2]Faculty of Business and Economics (HEC), Department of Operations, University of Lausanne, [3]Medical Direction, University Hospital of Lausanne, Lausanne, Switzerland

Background: Patient congestion is a strategic issue for many public hospitals. Consequences are boarding, diversion, and operating at high occupancy rate (*figure 1*). The aim of our work is to understand congestion in both medical and operations management perspective and how to reduce it without increasing capacity. We are focusing on our 193-beds internal medicine department (IMD) and considering congestion as an imbalance between needs of hospitalization (demand) in emergency department (ED) and available beds in IMD (supply).

Method: We aggregated administrative data over 3 years to identify factors of congestion crisis, including data such as length of stay (LoS), beds usage, and human resource usage. We used "warning emails" disseminated by executive management as indication of congestion crisis. We developed a model to predict congestion 2 days before it happens. Our approach was to fit a logistic regression model with a derivation cohort of 700 days and a validation cohort of 394 days.
Results: Collected data include 12'150 stays between 2011 and 2013. 91.3% of patients are admitted throught ED. We observe that variability of demand lies in: admission rate (average 13.5 per day; standard deviation, SD 5.7), LoS for same diagnostic group (SD 0.27 to 125.81 days), and complexity for same diagnostic group (SD 0 to 10.75). Variability of supply depends mainly on waiting beds for rehab (average 20.38; SD 6.81) decreasing exploited curative beds. Worked hours aren't correlated to occupancy rate, and therefore demonstrate flexibility of human resource.
For the prediction model, relevant variables are day of the year, month, number of patients exceeding 36 hours in the observation unit, total time of all patients spent in IMD on the day, average LoS of patients currently in IMD, and median LoS of patients discharged on the day. With the selected cutoff, our model shows sensitivity at 69.5% and specificity at 80.0% Area under the ROC curve is 0.81 (*figure 2*).
Conclusion: Matching high variabilities of demand and supply is the main challenge. Both have to be measured and transparently disseminated to all stakeholders. As admission rate and waiting beds can't be internally reduced, managing LoS is the key factor. Our short prediction model could help to increase supply by anticipating discharges.

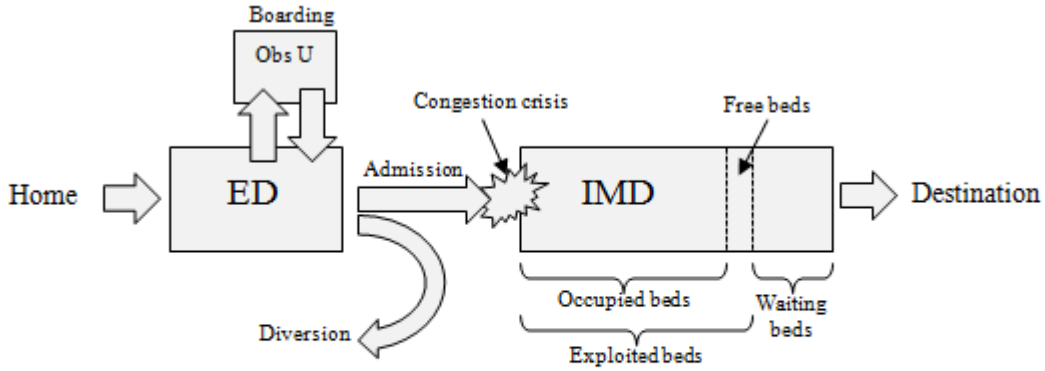


Figure 1: Simplified patient flow. 91.3% of IMD patients are admitted through ED. In absence of available bed in IMD, patients are "boarded" in an observation unit (Obs U), or inadequately "diverted" to other hospitals, home, or other destinations. Waiting beds for rehab or nursing homes reduce exploited beds available for curative care.

[Figure 1]

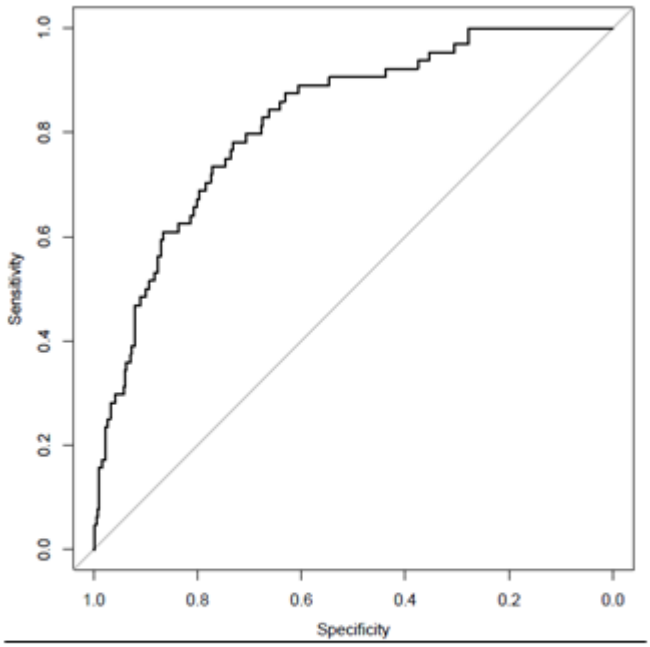


Figure 2: Receiver Operating Characteristic (ROC) curve of our model predicting congestion crisis. The area under the curve (AUC) is calculated to 0.82. More development is needed to adjust the model.

[figure 2]

FM276 **13 months of multimodal discharge plan for patients with heart failure: preliminary results of the LEAR-HF study**

Antoine Garnier[1], Sylvie Furrer[1], Nicole Bonvin[1], Véronique Prudent[1], Carole Nachar[2], Nathalie Rouiller Larpin[1], Estelle Lécureux[3], Pierre Voirol[2], Lilli Herzig[4], Anne-Claude Griesser[3], Gérard Waeber[1], Olivier Lamy[1]
[1]Internal Medicine Department, [2]Pharmacy Department, [3]Medical direction, University Hospital of Lausanne, [4]Institute of General Medicine (IUMG), University of Lausanne, Lausanne, Switzerland

Background: Readmission rate of patients with heart failure reached 19.5% within 30 days in 2012. We hypothesized that a discharge plan (DP) would reduce by 50 percent the number of days of early readmissions. Thanks to a SGIM-foundation grant, we created and applied a DP for selected patients in our tertiary internal medicine department for 13 months. We here present selected preliminary results.
Method: We developed our multimodal DP with inhospital partners and general practitioners. DP team consisted of a nurse, a clinical pharmacist, and a physician. We included consecutive hospitalized patients with symptomatic heart failure discharged at home. The study was based on before-after design on administrative records. The pre-intervention group consisted of 1464 cases between 2010 and 2013. The primary endpoint was the number of hospitalization days within 30 days after discharge, defining early readmission. Secondary endpoints included potentially avoidable readmissions (REAPE), and rate compared to expected ratio according to SQLape® computerized algorithm from routine administrative data.
Results: Starting November 2013, 3'318 cases have been screened on a daily basis (*table 1*). The main challenges were discharge before inclusion (109 cases) and change of destination after inclusion (35 cases). 141 patients received the discharge plan. Feedbacks from patients were widely positive. Therapeutic education and follow-up calls were performed in 96 to 99 percent of cases. Medication reconciliation at discharge was more difficult to complete (70%). Primary endpoint shows a non-significant reduction from 13.08 to 12.62 days of readmission per case. (p=0.764). Secondary endpoint shows a significant reduction of REAPE mean days from 2.06 to 1.14 days (- 44.6%, p=0.018). With a reduction of the rate from 11.29% to 8.95% (p=0.191), REAPE now lies in the expected margin of 9.11% ± 0.69 (*figure 1*).
Conclusions: Preliminary results do not quite confirm our hypothesis but are nevertheless encouraging. Statistical analyses have to be completed with the latest included patients, and numerous confounding factors

still have to be discussed. Gathered experiences showed the importance to identify early eligible patient and to have an early discharge date, while completing the entire DP.

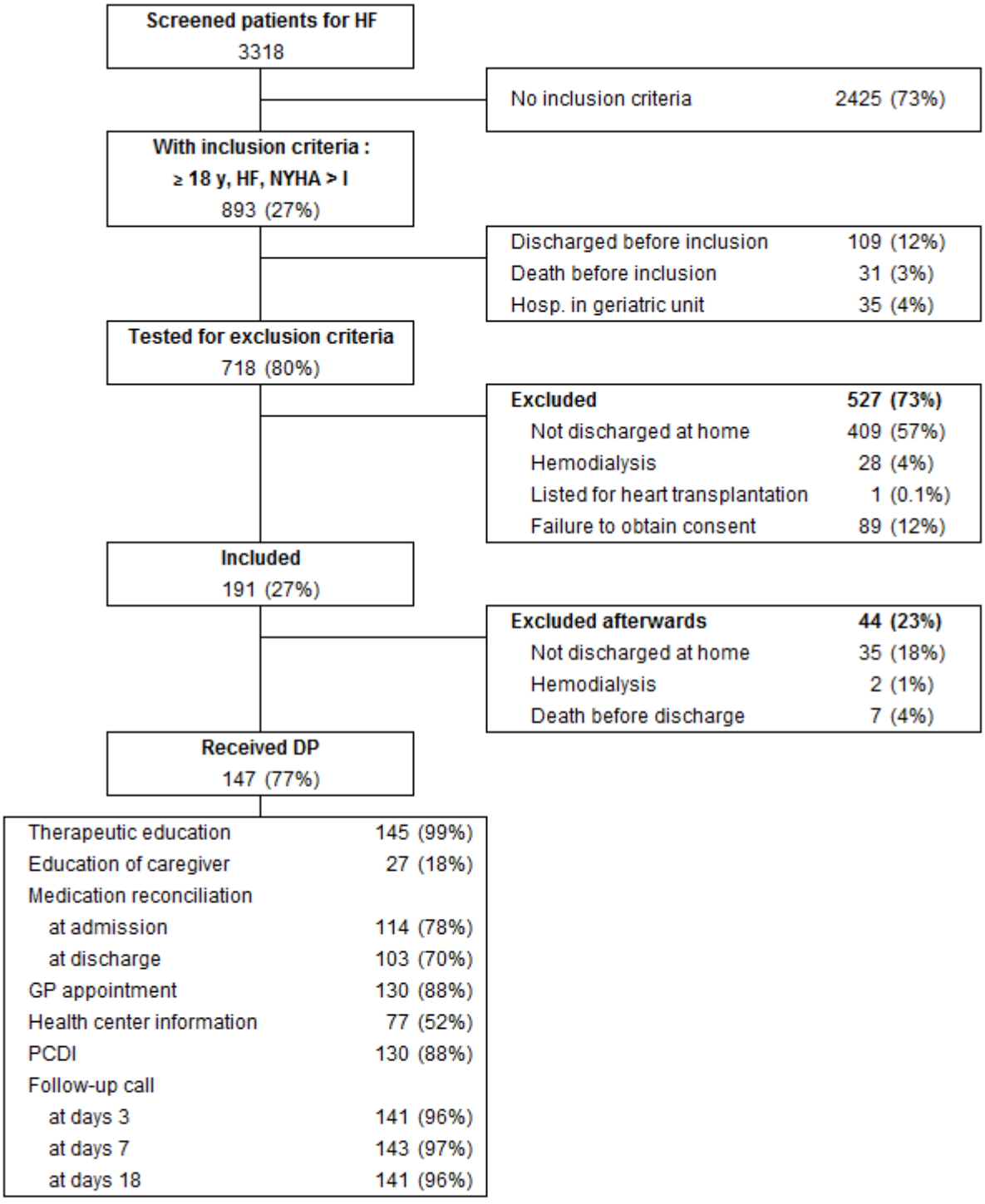


Table 1: Flowchart of LEAR-HF study. *Inclusion criteria are adult patient, hospitalized in internal medicine, and symptomatic heart failure (NYHA > I). Perform rates of each intervention are detailed in the bottom box. HF: Heart failure; NYHA: New York Heart Association classification; DP: discharge plan; PCDI: Patient-Centered Discharge Instructions.*

[Flowchart of LEAR-HF study]

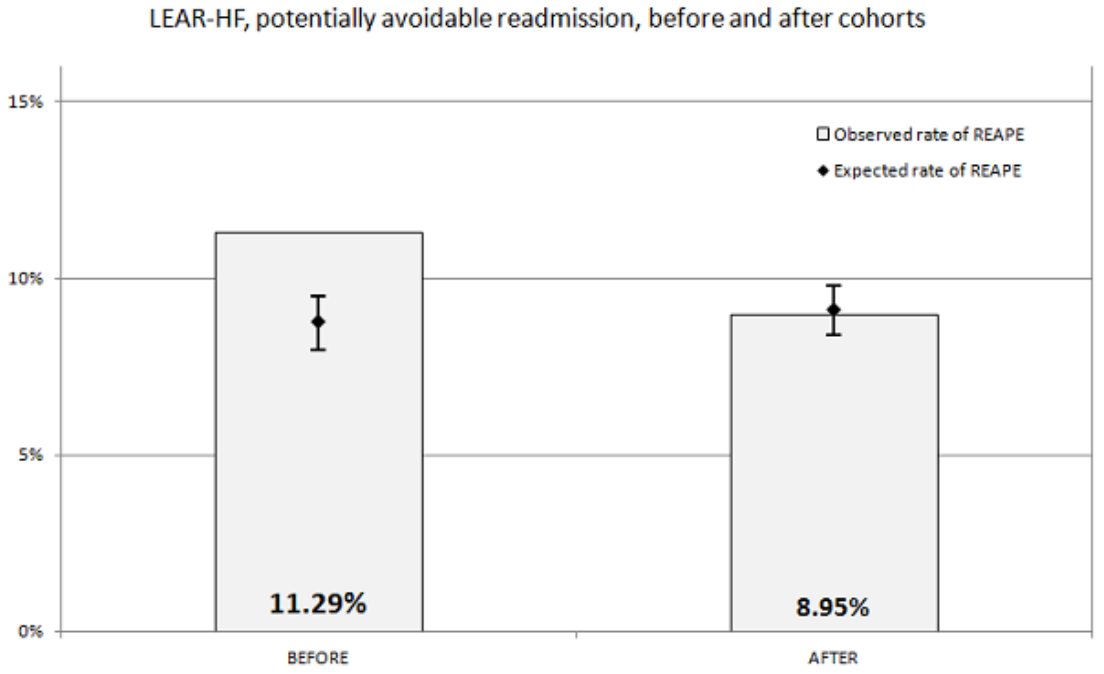


Figure 1: Although reduction of the rate of potentially avoidable readmission (REAPE) is not significant (p=0.191), it now lies in the expected margin of 9.11% + 0.69 estimated by SQlape®. Numerous confounding factors still have to be discussed. We counted 1435 eligible cases in the before cohort and 380 in the after cohort.

[Figure 1]

Freie Mitteilungen SGIM: Kardiologie / Pneumologie / Gastroenterologie

Communications libres SSMI: Cardiologie / Pneumologie / Gastroentérologie

FM277 Medical costs per QALY of statins using the Swiss Medical Board (SMB) assumptions: observed effects in two large primary prevention cohorts from Germany and Switzerland

Michel Romanens[1], Franz Ackermann[1], Thomas Szucs[2], Isabella Sudano[3], Ansgar Adams[4]
[1]Vascular Risk Foundation (Varifo), Olten, [2]European Centre of Pharmaceutical Medicine (ECPM), Basel, [3]University Heart Center Cardiology, University Hospital Zürich, Zürich, Switzerland, [4]Gesundheitsvorsorge und Sicherheitstechnik GmbH, Bonn, Germany

Background: The European Society of Cardiology (ESC) calculator defines 5% for fatal AMI in 10 years as high risk. We measured sensitivity (SENS) and specificity (SPEC) of different ESC risk levels in Switzerland (CH) and Germany (DE), where an atherosclerosis equivalent for ESC risk of 5% or more was available.
Methods: SMB assumptions: for 1 fatal AMI, 4.5 non-fatal AMI occur; relative risk reduction per 1 mmol/l LDL is 22%; cost per fatal AMI is CHF 8'500, per non-fatal AMI is CHF 25'000 in the first year and CHF 8'000 in subsequent years, loss of QALY is 1.0 for fatal and 0.2 for non-fatal AMI and annual preventive medical cost per individual including statin costs is CHF 470; all AMI events occur uniformly after 50% of the total observation time. We calculated a) costs for 5 and 10 years and b) a discrete Markov model for annual events with a linear occurrence of events over time; we used total carotid plaque area (TPA) ≥80 mm^2 (TPA80) to define high long-term (≥20% in ≥10 years) coronary risk (Arterioscler Thromb Vasc Biol. 2014;34:226-230) in Swiss (CH) and German (DE) healthy practice based subjects. From this, we derived SENS and SPEC for various ESC risk cutoffs for TPA80. An NNT of 25 was used as a clinically reasonable cutoff for statin intervention.

Results: Baseline characteristics: CH and DE N=1601 and N=2633, mean age 55±7 and 49±7 years respectively; TPA ≥80 mm^2 18% and 18%, respectively. For CH and DE, SENS and SPEC to detect TPA80 was, respectively: for ESC 1.8%: 45%/83% and 30%/94%; for ESC 3.3%: 15%/95% and 6%/99%; for ESC 5%: 4%/99% and 1%/100%; for ESC 7.5%: 1%/100% and 0.2%/100%.

Calculator: www.varifo.ch/QALYVarifo.xlsx	SMB QALY Model		Markov Model	
Costs (CHF) per QALY	5 years	10 years	5 years	10 years
NNT 45: ESC Risk at 5/10 years = 0.9%/1.8%	210´279	95´666	252´140	90´901
NNT 25: ESC Risk at 5/10 years = 1.65%/3.3% (VARIFO)	99´449	40´251	116´808	37´182
NNT 17: ESC Risk at 5/10 years = 2.5%/5.0%	53´110	17´081	60´224	14´722
NNT 11: ESC Risk at 5/10 years = 3.75%/7.5% (SMB)	23´126	2´089	23´611	189

[QALY Calculator using 5- and 10-year risk models]

Conclusion: We found statins to have costs per 1 mmol/l of LDL reduction of CHF 40'000/QALY (NNT 25) for an ESC risk of 3.3%. With ESC 7.5% (SMB guide), many subjects with confirmed high-risk atherosclerosis would not be treated (SENS 1% in CH, 0.2% in DE). Further studies are needed to test the SMB statin assumptions in the real world and to calculate costs per QALY with inclusion of medical *and* social costs.

FM278 Very long-term outcome of octogenarians after primary percutaneous coronary intervention for ST segment elevation myocardial infarction

Tiago Correia[1], Juan-Fernando Iglesias[2], Stéphane Fournier[2], Christan Roguelov[2], Nathalie Lauriers[2], Olivier Müller[2], Eric Eeckhout[2]
[1]Université de Lausanne / Ecole de médecine, [2]Lausanne University Hospital, Lausanne, Switzerland

Background: Primary percutaneous coronary intervention (pPCI) is nowadays the preferred ST segment elevation myocardial infarction (STEMI) treatment with a IA level of evidence according to international guidelines. Its benefits have been widely proven but are still uncertain concerning some specific populations ; elderly patients are one of these.
Demographic changes in developed countries are currently aging the global population. Parallel with life expectancy, the average STEMI patient age up.
The aim of the current study was to investigate long-term survival after pPCI for STEMI in patients who have lived beyond the age of life expectancy in Switzerland as data on this subject are currently lacking.
Methods: All octogenarians undergoing pPCI as STEMI treatment from 2008 to 2011, according to our institution's STEMI database, were retrospectively enrolled in this study ; no specific exclusion criteria. Demographic characteristics, procedural details and in-hospital events were observed from the medical records and/or STEMI database. Long-term survival was established by contacting the administrative authorities of the last known address of each patient. Primary endpoint was all-cause three-year mortality. Secondary endpoints were procedural success (defined as complete distal reperfusion and absence of any other complication) and in-hospital major events.
Results: 108 patients matched the inclusion criteria. 5 patients were excluded for geographical reasons. Mean age was 84.3 years, 51.5% of them were female. Majority had a 2 or 3 vessel disease (63%) and 23% presented ≥ 3 cardiovascular risk factors. Mean peak of creatine kinase level was 1930 U/l.
Procedural success was 93%. In-hospital death occurred in 11 patients (10%). Mean left ventricular ejection fraction at discharge was 46.5%.
Three-year mortality exceeded 32% and more than one third of the deaths occurred in the first month following the treatment.
Conclusion: The present study demonstrates an unexpectedly high long-term mortality rate in patients who

have lived beyond life expectancy and undergo pPCI for STEMI. The acute phase following the infarction seems to be the deadliest. Further research is necessary to confirm our observations.

FM279 Reliability of an ECG-algorithm for identification of the infarct-related artery in inferior myocardial infarction in clinical practice

Beate Buchmann[1], Tim Rönz[1], Thomas Fehr[2], Piero O. Bonetti[1]
[1]Division of Cardiology, Department of Internal Medicine, [2]Department of Internal Medicine, Kantonsspital Graubünden, Chur, Switzerland

Introduction: The presence of ST-segment elevation in lead III exceeding that in lead II, particularly when combined with ST-segment depression in lead I, aVL or both, has been proposed as a powerful predictor of occlusion of the right coronary artery with sensitivity/specificity values of 90% and 71% and positive/negative predictive values of 94% and 70% in patients with acute inferior myocardial infarction. The present study was performed to investigate the reliability of this algorithm in clinical practice.
Methods: The ECGs of all consecutive patients who presented to our hospital with acute inferior myocardial infarction and underwent emergency coronary angiography/primary percutaneous coronary intervention between January 2006 and December 2013 were analyzed retrospectively by 2 independent cardiologists according to the criteria mentioned above. The results were then compared with the angiographic findings.
Results: A total of 356 patients with acute inferior myocardial infarction were included in the present study. The infarct-related artery was the right coronary artery in 272 (76.4%) patients and the left circumflex coronary artery in 76 (21.4%) patients, whereas inferior myocardial infarction was caused by occlusion of the left anterior descending coronary artery in 4 (1.1%) and of the ramus intermedius in 4 (1.1%) patients. In our population the sensitivity/specificity values of the criteria above to correctly identify the right coronary artery were 78% and 49%, whereas the positive/negative predictive values were 83% and 41%.
Conclusion: In the present study we could not reproduce the excellent diagnostic accuracy of an electrocardiographic algorithm for predicting the infarct-related artery in acute inferior myocardial infarction reported in the literature. Thus, given its suboptimal diagnostic reliability and the lack of therapeutic consequences in patients with acute inferior ST-segment elevation myocardial infarction and a clear indication for emergency coronary angiography/primary percutaneous coronary intervention, the clinical relevance of the proposed criteria is questionable.

FM280 Colchicine for prevention of cardiovascular events: a systematic review and meta-analysis

Hannah Ewald, Viktoria L. Gloy, Dominik Glinz, Kelechi K. Olu, Armon Arpagaus, Alain J. Nordmann, Matthias Briel, Lars G. Hemkens
Institute for Clinical Epidemiology and Biostatistics, Basel, Switzerland

Background: Colchicine is an inexpensive drug with strong anti-inflammatory effects which might inhibit the inflammatory mechanisms leading to the development or destabilization of atherosclerotic plaques. There is so far no systematic review of the available evidence on the effects of Colchicine treatment on cardiovascular events that would allow a valid assessment of the potential long-term benefits and harms.
Purpose: To systematically evaluate potential benefits and harms of a continuous long-term treatment with Colchicine to prevent cardiovascular events in people with and without previous cardiovascular events following the methods of the Cochrane Collaboration.
Methods: All methods have been pre-specified in a design paper. We systematically searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE from inception to November 2014, ClinicalTrials.gov and the WHO Trials Registry Platform. We checked reference lists of all eligible studies and articles citing key papers in this area of research for additional studies and we contacted authors of included studies.
We included randomized and pseudo-randomized controlled trials published as full-text, abstract, and

unpublished data. We included trials in adults with any condition or disease comparing treatment with Colchicine (for at least 6 months, at any dose and with any type of application) with any non-Colchicine treatment. The primary outcomes were all-cause mortality, myocardial infarction and adverse events. Secondary outcomes were cardiovascular mortality, stroke, heart failure, non-scheduled hospitalizations and non-scheduled cardiovascular interventions.
Results: We have screened 2260 titles and abstracts and assessed 198 full text publications for eligibility. We included 38 studies. Preliminary analyses (data verification and author contacting undergoing) indicate an overall reduction of mortality in secondary prevention of cardiovascular disease by 52% (OR 0.48; 95% CI 0.23; 1.02). In patients with any condition and without a specific cardiovascular risk profile, we found an overall reduction of mortality by 10% (OR 0.90, 95% CI 0.74; 1.10). Colchicine leads to more gastrointestinal side effects (OR 1.82; 95% CI 1.02; 3.25) than control treatments. Definite results will be presented at the meeting.
Conclusions: Should our definite analyses confirm those results, Colchicine would be a very promising treatment for secondary prevention of cardiovascular disease.

Freie Mitteilungen SGIM: Beste Freie Mitteilungen

Communications libres SSMI: Meilleures communications libres

FM281 Thrombophilia and risk of recurrent venous thromboembolism: a multicenter prospective cohort study in elderly patients

Marie Méan[1,2], Andreas Limacher[3], Anne Angelillo-Scherrer[4,5], Lorenzo Alberio[6], Claire Abbal[6], Pierre Fontana[7], Bernhard Lämmle[4,8], Drahomir Aujesky[1]
[1]Department of General Internal Medicine, Bern University Hospital, Bern, [2]Department of General Internal Medicine, Lausanne University Hospital, Lausanne, [3]CTU Bern, Department of Clinical Research, and Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, [4]University Clinic of Hematology and Central Hematology Laboratory, University Hospital and the University of Bern, [5]Department of Clinical Research, University of Bern, Bern, [6]Service and Central Laboratory of Hematology, Lausanne University Hospital, Lausanne, [7]Division of Angiology and Haemostasis, Geneva University Hospital, Geneva, Switzerland, [8]Center for Thrombosis und Hemostasis, University Medical Center, Mainz, Germany

Background: The prognostic value of thrombophilia testing for venous thromboembolism (VTE) recurrence is unclear in the elderly because clinical factors, such as age and comorbid conditions, may be stronger drivers of recurrent VTE than biological thrombophilic risk factors. We aimed to evaluate the prevalence of biological thrombophilic risk factors and whether these factors were associated with recurrent VTE in a prospective multicenter cohort study of elderly patients (pts) with acute VTE.
Methods: We followed-up 650 in- and outpatients aged ≥65 years with symptomatic VTE from 9 Swiss university and non-university hospitals (09/09-12/13), starting 12 months after the index VTE. All pts were screened for factor (F)V Leiden and prothrombin G20210A mutations at baseline, and for fibrinogen, homocysteine, antithrombin, protein C, protein S, and coagulant activity of FVIII, FIX, and FXI levels as well as for anti-phospholipid antibodies (lupus anticoagulant, anticardiolipin and beta2-glycoprotein I IgG/IgM) in a fasting blood sample 12 months after the index VTE. Our outcome was VTE recurrence adjudicated by a committee blinded for the results of thrombophilia testing. We examined the association between biological thrombophilic risk factors and VTE recurrence, adjusting for pts characteristics (age, gender, prior VTE, type of VTE) and periods of anticoagulation as a time-varying co-variate.
Results: Of 650 pts, 442 (68%) had unprovoked VTE and 448 (69%) ≥1 biological thrombophilic risk factor. After a mean follow-up period of 21 months, 60 pts (9.2%) experienced a recurrent VTE, corresponding to an incidence rate of 5.5 events (95% confidence interval [CI] 4.3-7.1) per 100 patient-years. The incidence of recurrent VTE did not differ according to the presence of biological thrombophilic risk factors, except for lupus anticoagulant and high anti-beta2-glycoprotein I IgM levels (17 and 16-fold increase in the incidence of VTE recurrence, respectively, see table).

	No. of recurrences/ No. of pts	Incidence rate (95% CI)	Crude SHR (95% CI)	Adjusted* SHR (95% CI)
Lupus anticoagulant				
Positive	2/2	89.5 (22-357)	16.23 (9.77 to 26.96)	11.82 (5.58 to 25.04)
Negative	58/648	5.4 (4.1-6.9)	1 (Ref.)	1 (Ref.)
High anti-beta2-glycoprotein I IgM (>40 U/mL)				
Yes	2/4	84.4 (21.1-337.3)	10.91 (2.47 to 48.20)	16.69 (5.01 to 55.56)
No	58/646	5.4 (4.1-6.9)	1 (Ref.)	1 (Ref.)
Abbreviations: SHR= sub-hazard ratio; CI= confidence interval; Ref.= reference				
*Adjusted for age, gender, prior VTE, type of VTE (unprovoked vs provoked vs cancer), and periods of anticoagulation as a time-dependent covariate.				

[Thrombophilic risk factors and VTE recurrence]
After adjustment, lupus anticoagulant and high anti-beta2-glycoprotein I IgM levels remained significantly associated with recurrent VTE. No other biological thrombophilic factor was associated with VTE recurrence.
Discussion: In elderly pts with predominantly unprovoked VTE, only lupus anticoagulant and high anti-beta2glycoprotein IgM levels were associated with recurrent VTE. Testing for most biological thrombophilic factors does not appear to carry any benefit in elderly pts with VTE.

FM282 Predicting recurrence in elderly patients with unprovoked venous thromboembolism: prospective validation of the updated Vienna Prediction Model

Tobias Tritschler[1], Marie Méan[1,2], Andreas Limacher[3], Nicolas Rodondi[1], Drahomir Aujesky[1]
[1]Inselspital, Bern University Hospital, Bern, [2]Lausanne University Hospital, Lausanne, [3]University of Bern, Bern, Switzerland

Background: The updated Vienna Prediction Model (VPM) has been developed to risk-stratify patients with unprovoked venous thromboembolism (VTE) according to their recurrence risk based on their sex, VTE location and D-dimer. We prospectively evaluated the accuracy of the updated VPM in identifying elderly patients with unprovoked VTE who are at low risk of VTE recurrence.
Methods: We followed-up 156 in- and outpatients aged >=65 years with symptomatic, unprovoked VTE from 9 Swiss university and non-university hospitals (09/2009-12/2013), starting 12 months after the index VTE. All patients had previously completed a 3 to 12-month course of anticoagulation. Unprovoked VTE was defined as the occurrence of deep vein thrombosis or pulmonary embolism in the absence of risk factors, such as active cancer, immobilization, major surgery, or estrogen therapy. All patients underwent quantitative D-dimer testing (ELISA, VIDAS®, bioMérieux, France). The outcome was the recurrence of symptomatic, objectively confirmed VTE within 12 and 24 months, adjudicated by a committee of three blinded clinical experts. We determined the proportion of patients classified as low risk (lowest quartile of predicted 12-month risk of VTE recurrence) according to the updated VPM and compared the proportion of VTE recurrence at 12 and 24 months between low- and higher-risk patients. We also assessed the discriminative power of the predicted 12-month risk of VTE recurrence by calculating the area under the receiver operating characteristic (ROC) curve for VTE recurrence at 12 and 24 months.
Results: The median age was 74 years and 41% of patients were women. The proportion of VTE recurrence was 11% after 12 months and 17% after 24 months. Patients with a predicted 12-month risk below 6.2% were classified as low-risk based on the updated VPM. The proportion of recurrent VTE at 12 months (13%

vs. 10%; P=0.767) and 24 months (15% vs. 17%; P=1.0) did not differ between low vs. higher-risk patients. The area under the ROC curve for predicting VTE recurrence at 12 and 24 months was 0.39 (95% CI 0.25 to 0.52) and 0.43 (95% CI 0.31 to 0.54), respectively.
Conclusions: In our prospective multicenter study of elderly patients with unprovoked VTE, the updated VPM did not discriminate between patients who developed recurrent VTE from those who did not. The updated VPM may not be suitable for identifying elderly low-risk patients with unprovoked VTE who do not benefit from extended anticoagulation.

FM283 Is thyroid dysfunction associated with anaemia?

Khadija M'Rabet-Bensalah[1], Michael Coslovsky[2], Christine Baumgartner[1], Tinh-Hai Collet[3], Wendy P. J. den Elzen[4], Robert Luben[5], Anne Angelillo-Scherrer[6], Drahomir Aujesky[1], Kay-Tee Khaw[5], Nicolas Rodondi[1]
[1]Department of General Internal Medicine, Inselspital, University Hospital of Bern, [2]Department of Clinical Research, Clinical Trial Unit (CTU), University of Bern, Bern, [3]Service of Endocrinology, Diabetes and Metabolism, University Hospital of Lausanne, Lausanne, Switzerland, [4]Department of Public Health and Pirmary Care, Leiden University Medical Center, Leiden, The Netherlands, [5]Department of Public Health and Pirmary Care, University of Cambridge Addenbrooke's Hospital, Cambridge, United Kingdom, [6]University Clinic of Haematology and Central Haematology Laboratory, Inselspital, University Hospital of Bern, Bern, Switzerland

Introduction: Anaemia and abnormal thyroid function are common disorders that often co-occur. Most guidelines mention that thyroid-stimulating hormone (TSH) should be measured in the work-up of anaemia. However, data on the association between thyroid dysfunction and anaemia are scarce.
Methods: In the population-based European Prospective Investigation of Cancer (EPIC)-Norfolk cohort, we examined 12,972 men and women. Hypothyroidism was defined as TSH >4.49 mIU/L, either subclinical (SHypo) with normal free thyroxin (FT4) or overt (OHypo) with low FT4, and hyperthyroidism as TSH < 0.45 mIU/l, either subclinical (SHyper) with normal FT4 or overt (OHyper) with elevated FT4. Anaemia was defined as haemoglobin (Hb) < 13 g/dL for men and < 12 g/dL for women. We examined the association between thyroid function and anaemia using linear regression models with adjustment for age and gender. After excluding common causes of anaemia, we compared the prevalence of anaemia in the different thyroid functionality groups.
Results: Among 12,972 participants, 55% were women and the mean age was 58.9 ±9.5 years. Prevalence of thyroid dysfunction was 1.7% OHypo, 5.6% SHypo, 0.6% OHyper, and 2.8% SHyper. Anaemia was observed in 1,058 participants (8.2%) and was more prevalent among those with thyroid dysfunction (10.3%) compared to those in euthyroid state (7.9%).
The risk of anaemia was increased for OHypo with an age and gender adjusted risk ratio (RR) of 1.55 [95% confidence interval (CI) 1.10, 2.18] and OHyper with RR 1.86 [CI 1.12, 3.10], but not for SHypo (RR 1.06 [CI 0.84, 1.35]) and SHyper (RR 1.07 [CI 0.77, 1.49]). Hb concentration was decreased in participants with both higher and lower TSH levels (p for quadratic pattern < 0.001) in age and sex adjusted analyses, but this association was only significant for participants with OHypo (Hb 0.19 g/dl lower [CI [-0.34, -0.04]).
After excluding common causes of anaemia, such as iron deficiency, inflammatory disease, and kidney disease, 8.8 % of participants with OHypo (p=0.048), 16.3% with OHyper (p=0.005), 5.6% with SHypo (p=0.49) and 3.78% with SHyper (p=0.60) had anaemia compared to 4.9% of the euthyroid participants.
Conclusion: Overt hypo- and hyperthyroidism, but not subclinical thyroid dysfunction, are associated with a higher prevalence of anaemia. Given these data from the largest population-based study on this issue, TSH measurement is likely indicated only after excluding other common causes of anaemia.

FM284 Prognostic performance of echocardiography in hemodynamically stable elderly patients with acute pulmonary embolism

Eveline Hofmann[1], Andreas Limacher[2], Marie Méan[1,3], Nils Kucher[4], Marc Righini[5], Beat Frauchiger[6], Juerg-Hans Beer[7], Joseph Osterwalder[8], Markus Aschwanden[9], Christian Matter[10,11], Martin Banyai[12], Michael Egloff[13], Olivier Hugli[14], Daniel Staub[9], Henri Bounameaux[5], Nicolas Rodondi[1], Drahomir Aujesky[1]
[1]Department of General Internal Medicine, Bern University Hospital, [2]Clinical Trials Unit, University of Bern, Bern, [3]Department of General internal Medicine, Lausanne University Hospital, Lausanne, [4]Division of Angiology, Bern University Hospital, Bern, [5]Division of Angiology and Hemostasis, Geneva University Hospital, Geneva, [6]Department of Internal Medicine, Cantonal Hospital of Frauenfeld, Frauenfeld, [7]Cantonal Hospital of Baden, Baden, [8]Emergency Department, Cantonal Hospital of St. Gallen, St. Gallen, [9]Division of Angiology, Basel University Hospital, Basel, [10]Division of Cardiology, Zurich University Hospital, [11]Institute of Physiology, University of Zurich, Zurich, [12]Division of Angiology, Cantonal Hospital of Lucerne, Lucerne, [13]Division of Angiology, Geneva University Hospital, Geneva, [14]Emergency Department, Lausanne University Hospital, Lausanne, Switzerland

Background: Evidence suggests that several echocardiographic signs of right ventricular dysfunction (RVD) are associated with an increased short-term mortality in hemodynamically stable patients with acute pulmonary embolism (PE). Cardiology guidelines recommend performing transthoracic echocardiography to risk-stratify such patients. Although elderly patients with PE have a higher complication rate than younger patients, the prognostic performance of transthoracic echocardiography to predict adverse outcomes has not been specifically examined in the elderly.
Methods: We studied 400 hemodynamically stable patients aged ≥65 years with acute PE in a Swiss prospective multicenter cohort study between September 2009 and June 2012. Transthoracic echocardiography was performed by blinded cardiologists within three days of PE diagnosis. We defined RVD as a right ventricular (RV)/left ventricular ratio >0.9 or RV hypokinesis (primary definition) or the presence of either ≥1 or ≥2 of 6 predefined echocardiographic signs of RVD (secondary definitions). Outcomes were overall mortality, the combination of mortality/non-fatal recurrent venous thromboembolism (VTE) and health-related quality of life at 90 days, and length of hospital stay. We examined the association between RVD and outcomes, adjusting for patient baseline characteristics.
Results: Overall, 36% of patients had RVD based on our primary definition, and 81% and 53% based on our secondary definitions, respectively. Using our primary definition, there was no association between RVD and mortality (adjusted HR 0.81, 95%CI 0.35-1.88), mortality/non-fatal VTE (adjusted HR 0.96, 95%CI 0.45-2.08), or quality of life. RVD was associated with an increased length of stay (adjusted time ratio 1.18, 95%CI 1.03-1.36). Using our secondary definitions, we found no association between RVD and clinical outcomes. However, RVD was associated with a poorer quality of life and a longer hospital stay.
Conclusions: The prevalence of echocardiographic RVD varied widely based on the criteria used to define RVD in elderly, hemodynamically stable patients with acute PE. We did not find an association between RVD and clinical outcomes but patients with RVD had a poorer health-related quality of life and a longer hospital stay. The assessment of echocardiographic RVD as a stand-alone risk stratification tool appears to be of uncertain usefulness in elderly, hemodynamically stable patients with acute PE.

FM285 Management of patients with possible familial hypercholesterolemia in the general population: room for improvement

David Nanchen[1], Pedro Marques-Vidal[2], Arnold von Eckardstein[3], Jacques Cornuz[1], Gerard Waeber[2], Vincent Mooser[2], Peter Vollenweider[2]
[1]Policlinique Médicale Universitaire (PMU), [2]CHUV, Unversité de Lausanne, Lausanne, [3]Institut für Klinische Chemie, Zurich, Switzerland

Background: Appropriate management of familial hypercholesterolemia (FH) is essential to avoid premature atherosclerosis. Although quality of care of patients with FH has been previously described in

lipid clinics, less is known for patients with FH in the general population.
Methods: We studied 5,937 adults aged 35-75 years not using lipid-lowering drugs from a population-based cohort study in Switzerland. Three algorithms based on LDL-cholesterol levels and familial/personal history of premature atherosclerosis, the Dutch Lipid Clinic (score >=3 points), the Simon Broome Register, and the latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines (LDL-cholesterol >4.9 mmol/l) were used to identify patients with a possible diagnosis of FH at baseline. The diagnosis of possible FH was not communicated to primary care physicians in charge of the patients. After 5.5-years follow-up, we assessed
1) appropriate lipid management, defined as any lipid-lowering drugs or LDL-cholesterol< 2.6 mmol/l or 50% decrease in LDL-cholesterol;

2) optimal lipid management, defined as use of high-intensity statins such as atorvastatine 40 mg or higher, or rosuvastatine 20mg or higher
3) ideal blood pressure, defined as < 140/90 mmHg; and
4) smoking cessation among smokers.
Results: Possible FH was diagnosed in 274 (4.6%) patients according to the Dutch Lipid Clinic algorithm. An additional 76 patients (1.3%) were identified using either the Simon Broome or the ACC/AHA guidelines. Among these 350 patients with possible FH, baseline mean (standard deviation) lipid levels were 5.2 (0.8) mmol/l for LDL-cholesterol, 1.5 (0.4) mmol/l for HDL-cholesterol and 1.7 (0.9) mmol/l for triglycerides. After 5.5 years follow-up, 13 patients died and 84 refused to participate. Among the remaining 253 patients alive and without missing data, 99 (39.1%) achieved appropriate lipid management, 6 (2.4%) achieved optimal lipid management, 164 (65.6%) had ideal blood pressure, and 18/81 (22.2%) smokers stopped. Over 5.5 years, mean absolute change in LDL-cholesterol levels was -0.9 (1.2) mmol/l. Baseline LDL-cholesterol levels, but not family history of premature atherosclerosis, were associated with appropriate lipid management.
Conclusion: In this population-based sample, over 60% of adults with a clinical diagnosis of possible FH are not appropriately treated after 5.5-years follow-up. Better implementation of the guidelines for managing FH by clinicians is urgently needed.

FM286 Impact of case management on frequent users' quality of life: a randomized, controlled trial

Katia Iglesias[1,2], Karine Moschetti[3,4], Stéphanie Baggio[5], Venetia Velonaki[6], Ornella Ruggeri[7], Olivier Hugli[8], Bernard Burnand[2], Jean-Blaise Wasserfallen[9], Jean-Bernard Daeppen[10], Patrick Bodenmann[7]
[1]Center for the Understanding of Social Processes, University of Neuchâtel, Neuchâtel, [2]Institute of Social and Preventive Medicine, Lausanne University Hospital, [3]Institute of Health Economics and Management, University of Lausanne, [4]Technology Assessment Unit, Lausanne University Hospital, [5]Life Course and Social Inequality Research Center, University of Lausanne, [6]Department of Community Medicine and Public Health, [7]Vulnerable Population Unit, Department of Ambulatory Care and Community Medicine, [8]Emergency Department, [9]Medical Directorate, [10]Alcohol Treatment Center, Lausanne University Hospital, Lausanne, Switzerland

Introduction: Frequent emergency department (ED) users are often vulnerable patients with many risk factors affecting their quality of life (QoL). The aim of this study was to examine to what extent a case management intervention improved frequent ED users' QoL.
Methods: Data were part of a randomized, controlled trial designed to improve frequent ED users' QoL at the Lausanne University Hospital. A total of 194 frequent ED users (≥ 5 attendances during the previous 12 months; ≥ 18 years of age) were randomly assigned to the control or the intervention group. Participants in the intervention group received a case management intervention (i.e. counseling and assistance concerning social determinants of health, substance-use disorders, and access to the health-care system). QoL was evaluated using the WHOQOL-BREF at baseline and twelve months later. Four dimensions of QoL were retained: physical health, psychological health, social relationship, and environment, with scores ranging from 0 (low QoL) to 100 (high QoL).

A linear, mixed-effects model with participants as a random effect was run to analyze the change in QoL over time. The effects of time, group, and their interaction were tested, controlling for socio-demographic characteristics and health-related variables.
Results: Participants were 45.5 (SD=17.9) years old on average; 56% were men; 50% Swiss, 18% European, and 32% non-European. Levels of QoL dimensions ranged on average between 54.1 and 58.9 (SD between 15.0 and 24.8).
Multivariate models showed an improvement in QoL for the four dimensions (physical health: b=8.1, p< 0.001; psychological health: b=9.5, p< 0.001; social relationship: b=13.9, p< 0.001; environment: b=10.1, p< 0.001). This improvement was significantly greater for the intervention group concerning the environment element (b=6.2, p=0.016).
Conclusion: The case management intervention was accompanied by improvement in frequent ED users' environment QoL—a dimension composed of items such as physical safety and security, financial resources, and access to health-care. This result shows the success of the case management to improve these aspects by providing assistance in obtaining income entitlements, health insurance coverage, stable housing, and schooling for children, and in preventing potential violence in the home and finding general practitioners or specialists. This study shows that environment QoL was a dimension that seems most suitable for short-term interventions.

Freie Mitteilungen SGIM : Allgemeine Innere Medizin 5

Communications libres SSMI: Médecine interne générale 5

FM287 Are thyroid stimulating hormone levels associated with an increased risk of atrial fibrillation? An individual participant analysis of large prospective international cohort studies

Christine Baumgartner[1], Bruno R. da Costa[2], Tinh-Hai Collet[3], Anne R. Cappola[4], Douglas C. Bauer[5], Daniel Segna[1], Hendrika Anette van Dorland[1], Carmen Floriani[1], Peter Jüni[2], Graziano Ceresini[6], Jacobijn Gussekloo[7], Wendy P. J. den Elzen[7], Robin P. Peeters[8], Henry Völzke[9], Marcus Dörr[10,11], John P. Walsh[12,13], Alexandra Bremner[14], Massimo Iacoviello[15], Ian Ford[16], Jan Heeringa[17], Susan R. Heckbert[18], David J. Stott[19], Rudi G. J. Westendorp[20], Drahomir Aujesky[1], Nicolas Rodondi[1]
[1]Department of General Internal Medicine, Inselspital, University Hospital of Bern, [2]Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Bern, [3]Service of Endocrinology, Diabetes and Metabolism, University Hospital of Lausanne, Lausanne, Switzerland, [4]University of Pennsylvania School of Medicine, Philadelphia, PA, [5]Departments of Medicine and Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA, United States, [6]Department of Clinical and Experimental Medicine, Geriatric Endocrine Unit, University Hospital of Parma, Parma, Italy, [7]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, [8]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands, [9]Institute for Community Medicine, Clinical-Epidemiological Research, [10]Department of Internal Medicine, University of Greifswald, [11]DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany, [12]School of Medicine and Pharmacology, University of Western Australia, Crawley, [13]Department of Endocrinology & Diabetes, Sir Charles Gairdner Hospital, Nedlands, [14]School of Population Health, University of Western Australia, Crawley, WA, Australia, [15]Cardiology Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy, [16]Robertson Center for Biostatistics, University of Glasgow, Glasgow, United Kingdom, [17]Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands, [18]Department of Epidemiology, University of Washington, Seattle, WA, United States, [19]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom, [20]Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

Introduction: Prospective data on the association between thyroid stimulating hormone (TSH) levels across the full range and atrial fibrillation (AF) are conflicting, and debate exists on the limits of the optimal TSH reference range and treatment targets. Some prospective studies have found subclinical hypothyroidism to be associated with a reduced risk of AF. Identification of modifiable risk factors of AF is important to optimize prevention. We aimed to assess the risk of AF across the full TSH range in all available prospective cohorts.
Methods: Individual participant data from 7 large prospective cohorts with thyroid function at baseline and incident AF outcomes were analyzed. Euthyroidism was defined as TSH level from 0.45 to 4.49mIU/l and subdivided into five categories (0.45-0.99, 1.00-1.49, 1.50-2.49, 2.50-3.49, and 3.50-4.49). We compared the incidence of AF of all TSH groups to the reference group 3.50-4.49. Subclinical hypothyroidism was defined as TSH level between 4.5 and 19.9 and subclinical hyperthyroidism as TSH level < 0.45, both with normal free thyroxine levels.
Results: Among 11,387 adults, 1064 (9.3%) had subclinical hyperthyroidism and 900 (7.9%) had subclinical hypothyroidism. In total, 962 individuals developed AF during follow-up. In individuals with subclinical hyperthyroidism, the risk of AF increased with lower TSH levels: age- and sex-adjusted hazard ratio (HR) 1.64 (95% confidence interval [CI] 1.07-2.53) for a TSH level of 0.10-0.44mIU/l and 1.71 (95% CI 0.69-4.26) for a TSH level < 0.10, p value for trend 0.024. The risk of AF events was not increased in TSH categories within the euthyroid range, with an HR of 1.16 (95% CI 0.86-1.56) for a TSH level of 0.45-0.99, HR 0.97 (95% CI 0.73-1.28) for a TSH of 1.00-1.49, HR 1.14 (95% CI 0.89-1.46) for a TSH of 1.50-2.49, and HR 1.07 (95% CI 0.82-1.39) for a TSH of 2.50-3.49 compared to a TSH level of 3.50-4.49. Subclinical hypothyroidism was not significantly associated with a lower risk of incident AF. Excluding patients with thyroid hormone medication at baseline yielded similar results.
Conclusion: Euthyroid individuals, even those with TSH levels within the low-normal range, are not at increased risk of developing AF, whereas the risk of AF increases with lower TSH levels in patients with subclinical hyperthyroidism. Subclinical hypothyroidism is not associated with a protective effect for AF. These data do not support changing the lower or upper limit of TSH based upon the risk of AF.

FM288 Hereditary angioedema in Switzerland: clinical characteristics and therapeutic modalities in 2012

Urs Steiner[1], Christina Weber[2], Arthur Helbling[1], Peter Schmid-Grendelmeier[2], Walter Wuillemin[3]
[1]Spitalnetz Bern, Bern, [2]Allergy Unit USZ, Zurich, [3]Division of Hematology, Lucerne, Switzerland

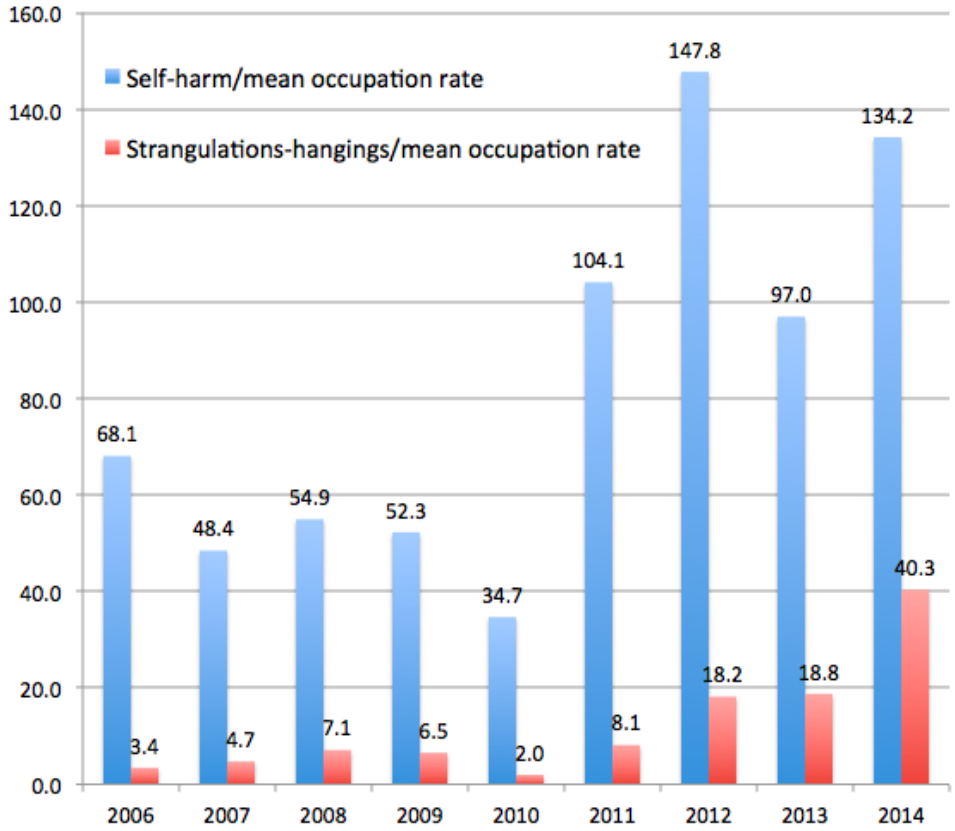
Background: Hereditary angioedema (HAE) is a rare, autosomal dominant disease due to deficiency of C1-esterase inhibitor (C1-INH). 127 HAE affected people are treated in the centers Lucerne, Zurich and Berne. In a retrospective cohort study we describe disease characteristics and treatment modalities of HAE patients in Switzerland for 2012.
Method: A questionnaire was sent to each patient including questions about clinical characteristics and treatment modalities.
Result: Median age of the 68 women and 59 men is 43 years, at symptom onset 11 years. 19 patients are younger twenty, 37 younger fourty, 45 younger sixty and 26 older than sixty years old. 119 patients suffer from type I, 2 from type 2 and 6 are not proven yet. 104 patients (57 women, 47 men) returned the questionnaire. 75% were symptomatic and experienced together 1780 attacks. 1300 by women, 480 by men. 30 women and 10 men suffered from > 1 attack/month. 68% suffered from abdominal attacks, 58.6% from edemas of the limbs, 21% each from attacks of the trunk, face and genitals and 15.4% each of head ache and laryngeal attacks. Main trigger factor is psychological stress/emotion (51%) followed by trauma/physical exertion 41%, hormonal influence 33%, infection 20%, foodstuffs 19% and allergies 12.5%. Therapeutic options in Switzerland include prophylaxis with tranexamic acid or danazol and therapy on demand with C1 Inhibitor (C1-INH) and Icatibant. Of the 78 symptomatic patients 30.7% were on prophylaxis, 57.7% without and 11.5% on IRT. Of the 26 asymptomatic patients 46% were on prophylaxis, 54% without. From the 26 patients on danazol, 38% were asymptomatic, 3.8% suffered from severe, 15.4% from moderate and 42% from rare attacks. From 59 patients without prophylaxis 23% were asymptomatic, 10.6% suffered from severe, 30.5% from moderate and 35.6% from rare attacks. 42% used therapy on demand with C1INH, 6.7% with Icatibant. 38 of 57 patients (65%) practise home treatment with C1-INH. 35.6% suffer from co-

morbidities. With 11% arterial hypertension is the most relevant, followed by dyslipidemia with 5.7%.
Conclusion: Clinical characteristics and therapeutic modalities of 104 swiss HAE patients indicate that symptoms, intensity of disease and therapy is very individual. Gastrointestinal and skin symptoms predominate. Women suffer from more frequent and more intense attacks. Prophylaxis with danazol is efficient but you have to consider side effects.

FM289 Self-harm among prisoners in Geneva, Switzerland

Hans Wolff[1], Alejandra Casillas[1], Thomas V. Perneger[2], Patrick Heller[1], Diane Golay[1], Elisabeth Mouton[1], Magali Morasz[1], Patrick Bodenmann[3], Laurent Gétaz[1]
[1]Division of Correctional Medicine and Psychiatry, [2]Division of Clinical Epidemiology, Hopitaux Universitaire de Genève, Genève, [3]Vulnerable Population Unit, CHUV, Unversité de Lausanne, Lausanne, Switzerland

Background and aim: Prison institutional conditions affect risk for self-harm among detainees. In particular, prison overcrowding may increase the likelihood of self-harm by creating competition for resources, space, and enhancing a "depravation state". This initial study examined the association between self-harm and overcrowding in Switzerland's largest prison.
Methods: This cross-sectional study took place at Champ-Dollon prison (Geneva, 2014 capacity: 384). We obtained information from a database kept by the prison medical unit. Poisson regression outcomes were
1) self-harm and
2) self-strangulation/hanging events.
Dichotomous predictors were overcrowding index- annual mean daily population divided by capacity (< 200% vs. >200%), and year group (2006-2009 vs. 2011-2014) (Table 1). Apart from this, we qualitatively examined public data, looking for patterns of change/instability in factors, which on their own could have affected/explained any change.
Results: Figure 1 displays the ratios of self-harm and self-strangulation/hangings divided by overcrowding indices for each year since 2006. Table 1 confirms that self-harm and self-strangulation/hanging significantly increased in 2011-2014 compared to 2006-2010 ($p < 0.001$). Overcrowding was associated to self-strangulation/hangings
($p < 0.001$), but self-harm rates were not ($p < 0.85$). In terms of pertinent demographics that would affect self-harm (data not shown), there was no prison change in gender, area of origin, foreign residency, or religion. There has been no increase in the number of prisoners receiving treatment for opiate addiction and psychiatric and psychological consultations in prison remained stable- despite rising incarcerations.
Conclusions: We observed an alarming increase in self-harm and particularly self-strangulation/hangings since 2011, and overcrowding is significantly associated with self-strangulation/hangings. Overcrowding can impose destructive effects on the psychological and behavioral well being of inmates in prison, influencing a myriad of emotional and livelihood factors that predispose to harmful behavior. Next steps should further examine the relation between self-harm, strangulation/hanging and overcrowding, adjusting for pertinent information from individual patient prison records. Urgent steps have to be taken to decrease overcrowding at Champ-Dollon prison in order to prevent self-harm and potential suicide.



[Fig.1: Ratio of self-harm by occupation rate]

FM290 Training primary care physicians in shared decision making for colorectal cancer screening. Insights from the first statewide colorectal cancer screening program in Switzerland

Reto Auer[1], Kevin Selby[1], Jean-Luc Bulliard[2], Cristina Nichita[3], Gachoud David[4], Gian Dorta[3], Cyril Ducros[5], Jacques Cornuz[1]
[1]Policlinique Médicale Universitaire (PMU), [2]Institut Universitaire de Médecine Sociale et Préventive (IUMSP), [3]Service de gastro-entérologie et d'hépatologie - CHUV, [4]Service de Médecine Interne - CHUV et Unité Pédagogique, Faculté de Biologie et de Médecine (FBM), UNIL, [5]Fondation vaudoise pour le dépistage du cancer, Lausanne, Switzerland

Background: The State of Vaud has launched the first population-based, organized, colorectal cancer screening program in Switzerland for the population aged 50 to 69. Each primary care physician (PCP) has been invited to participate in an interactive session preparing them to enroll patients in the screening program. We aimed at testing the impact of an interactive seminar for PCPs on their intention to discuss the options of no screening, screening with the fecal-immunological test (FIT) and colonoscopy.
Methods: We measured attitude, intentions and knowledge through questionnaires filled by PCPs before and after a 2.5 hour-long interactive seminar. The main outcome was the proportion of physicians foreseeing to offer coloscopy vs FIT on an equal basis. Physicians estimated the proportion of their patients prescribed a fecal occult blood test (FOBT) vs coloscopy over the months before the seminar and after the interactive seminar. We used a clinical vignette to test for knowledge about screening indications. The interactive seminar included powerpoint presentations with quizzes and clickers, an 8-minute video presenting a shared decision making (SDM) consultation around CRC screening and distribution of educational materials such as a SDM decision aid and background epidemiological information.
Results: 93 PCPs participated in two training seminars. 57(63%) PCPs responded before and 70(75%) after the training seminars. Before the seminar, 9% of physicians reported having prescribed colonoscopy compared to FIT in about similar proportions; after the seminar, 37% of PCP were foreseeing prescribing both exams in similar proportions (absolute difference 29%, adjusted relative risk 4.3, 95% CI:1.7 to 10.5,

p< 0.001). No PCP reported taking the decision about screening alone and the proportion preferring SDM as a preferred communication style did not change significantly (46% vs 44%, P=0.1). The proportion adequately offering CRC screening the patient in the clinical vignette increased from 81% to 98% (p=0.04).
Conclusion: An interactive seminar training PCPs to enroll patients into a CRC screening program significantly increased the proportion foreseeing to offer FIT and colonoscopy on an equal basis and increased knowledge about indications for screening. Future studies should aim at measuring the impact of the program on PCPs real life practice and on patient's stated involvement in screening decisions.

Gastgesellschaft SFGG: Freie Mitteilungen

Société conviée SPSG: Communications libres

FM291 Instrumented shoes for activity monitoring in the elderly: measurement system and in lab validation

Christopher Moufawad el Achkar[1], Kristof Major[2], Constanze Lenoble Hoskovec[2], Anisoara Paraschiv Ionescu[1], Helene Krief[2], Christophe Bula[3], Kamiar Aminian[1]
[1]EPFL, [2]Geriatrie, CHUV, Université Lausanne, [3]CHUV, Unversité de Lausanne, Lausanne, Switzerland

Background: Monitoring daily activity levels in elderly persons is gaining interest, in particular in the context of the prevention of fall and frailty. A wearable system placed entirely at the shoe level that measures the force under the foot via an insole and the foot movement via inertial sensors was developed to achieve this aim. The objective of this study was to determine the accuracy of activity classification in a sample of community-dwelling older persons.
Methods: Ten healthy elderly participants aged 65 or older participated in the study. They wore instrumented shoes (Figure) consisting of an insole (IEE, LU) and Physilog inertial measurement unit (GaitUp, CH). Using a standardized protocol, measurements were performed over an hour and included walking, sitting, standing, postural transitions, stairs and up/downhill walking activities. A biomechanical rule-based approach was used to build a hierarchical algorithm to classify each activity recorded. For validation, each subject wore simultaneously a reference system consisting of an inertial sensor on the thigh and the trunk [1].

[Figure: Instrumented shoe system]
Results: Accuracy with respect to the reference system averaged 97% (Table), with sensitivity ranging from 89% (walking, upstairs) to 100% (walking downhill). Periods of upstairs/downstairs, uphill/downhill, as well as postural transitions (sit-to-stand and stand-to-sit) were all correctly classified.

Activity	Sensitivity	Specificity	Precision
Sitting	0.99	1	1.00
Standing	0.96	1	0.96
Walking	0.96	1	0.95
Walking Upstairs	0.89	1	0.99
Walking Downstairs	0.94	1	0.98
Walking Uphill	0.94	1	0.96
Walking Downhill	1.00	1	0.98
Elevator Up	0.97	1	0.79
Elevator Down	0.90	1	0.78

[Table: Sensitivity, specificity, precision and ove]

Conclusions: These results show that the system and the developed algorithm provided activity classification with high accuracy. Next step is the validation in daily life conditions over longer periods. The system can potentially be used for activity monitoring in other populations and also for instrumented mobility tests.

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement FARSEEING n° 288940.

Bibliography: [1] A. Paraschiv-Ionescu,et al. *Gait Posture*, vol. 20, no. 2, pp. 113-25, Oct. 2004.

FM292 Foot clearance in older persons: a new indicator of fall risk

Christophe Bula[1], Kristof Major[1], Constanze Lenoble Hoskovec[1], Fabiana Botrugno[2], Laurence Seematter Bagnoud[1], Farzin Dadashi[3], Helene Krief[1], Chantal Piot Ziegler[4], Kamiar Aminian[3], Brigitte Santos Eggimann[2]
[1]Gériatrie CHUV, Université de Lausanne, [2]IUMSP, CHUV, Lausanne, [3]EPFL, [4]Psychologie, Université de Lausanne, Lausanne, Switzerland

Background: Foot clearance during the swing phase of walking has been linked to tripping and falling. In particular, increased variability of minimum foot clearance has been associated with retrospective falls in one former study. However, the relationship between other parameters of foot clearance and prospective falls has not yet been investigated.

Methods: Eligible participants were those enrolled in the first wave of the Lc65+ cohort study, a population based cohort launched in 2004 to study frailty. They were aged 73 to 77 years at the time of gait assessment that was performed over a 20 meters walkway at self-selected pace, using footworn sensors. In addition to usual gait parameters (speed and stride length), specific foot clearance parameters that were evaluated included maximal and minimal heel and toe clearances, as well as their variability. Falls were collected prospectively over a 12-month follow-up period using a monthly fall calendar. Participants included in the present analysis were those who a) underwent a full gait assessment; b) completed all 12 fall card reporting.

Results: Among participants (N=794, mean age 75.0±1.4 years, 58.4% women, 39.3% living alone, 3.9% with MMSE score < 24, 86.8% reporting no difficulty in their basic ADLs), 29.4% reported one or more falls over the 12-month follow-up period. Compared to the others, participants reporting one or more falls had decreased gait speed (1.18±0.17 vs 1.20±0.19 m/sec, p=.038) and stride length (1.23±0.15 vs 1.26±0.17 m, p=.009). They also had decreased maximal heel (28.7±3.8 vs 29.3±3.9 cm, p=.014) and maximal toe (12.5±3.0 vs 13.3±3.3 cm, p=.002) clearance. In contrast, minimal toe clearance did not vary across fall categories (1.8±0.7 vs 1.8±0.8 cm, p=.993).

Conclusion: In this large, representative, cohort of community-dwelling older persons, maximal heel and toe clearance were both associated with subsequent falls over the 12-month follow-up period, whereas minimal toe clearance was not. Likely, maximal heel and toe clearance reflect lower limb strength and future studies should investigate whether these parameters will be sensitive to strengthening interventions designed to reduce fall risk.

FM293 Comparative performance of current definitions of sarcopenia against the prospective incidence of falls among community-dwelling seniors age 65 and older

Heike A. Bischoff-Ferrari[1,2], J E Orav[3], J A Kanis[4], R Rizzoli[3], M Schlögl[1,2], H B Staehelin[5], W C Willett[6], B Dawson-Hughes[7]
[1]Dept. of Geriatrics, University Hospital Zurich, [2]Centre on Aging and Mobility, University of Zurich, Zurich, [3]Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland, [4]Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, United Kingdom, [5]Dept. of Geriatrics, University of Basel, Basel, Switzerland, [6]Dept. of Nutrition, Harvard School of Public Health, [7]USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, United States

Aim: To compare the extent to which 7 available definitions of sarcopenia and 2 related definitions predict the prospective rate of falling.
Methods: We studied a cohort of 445 seniors (mean age 71 years, 45% men) living in the community who were followed with a detailed fall assessment for 3 years. For comparing the rate of falls in sarcopenic versus non-sarcopenic individuals, we used multivariate Poisson regression analyses adjusting for gender and treatment (original intervention tested vitamin D plus calcium against placebo). Of the 7 available definitions, 3 were based on low lean mass alone (Baumgartner, Delmonico1 and 2) and 4 required both low muscle mass and decreased performance in a functional test (Fielding, Cruz-Jentoft, Morley, Muscaritoli). The 2 related definitions were based on low lean mass alone (Studenski1) and low lean mass contributing to weakness (Studenski2).
Results: Among 445 participants, 231 fell, sustaining 514 falls over the 3-year follow-up. The prospective rate of falls in sarcopenic versus non-sarcopenic individuals was best predicted by the Baumgartner definition based on low lean mass alone (RR = 1.54; 95% CI: 1.09-2.18) with 11% prevalence of sarcopenia and the Cruz-Jentoft definition based on low lean mass plus decreased functional performance (RR = 1.82; 95% CI: 1.24-2.69) with 7.1% prevalence of sarcopenia. Consistently, fall rate was non-significantly higher in sarcopenic versus non-sarcopenic individuals based on the definitions of Delmonico1, Fielding and Morley.
Conclusion: Among the definitions investigated, the Baumgartner definition and the Cruz-Jentoft definition had the highest validity for predicting the rate of falls.

FM294 Gerontotraumatologie: Erfahrungen mit einem chirurgisch - geriatrischen Co-Management einer Risikopopulation

Sacha Beck, Marlis Nardi, Michael Dietrich, Elisabeth Mattle
Innere Medizin FMH, spez. Geriatrie, Zentrum für Gerontotraumatologie, Stadtspital Waid, Zürich, Switzerland

Hintergrund: Die medizinische Betreuung von geriatrischen Patienten im Akutspital ist komplex. Die Bedürfnisse unterscheiden sich stark von denjenigen junger Patienten. Krankheiten präsentieren sich im Alter oft untypisch und sind deshalb schwieriger zu erkennen. Das Ansprechen auf medizinische Interventionen ist schwierig vorauszusehen und es treten häufiger Komplikationen auf. Speziell in der Chirurgie stellen sich deshalb für die Behandlungsteams grosse Herausforderungen, die sich im Licht der Zunahme operativ versorgter, betagter Patienten akzentuieren werden. Die Vernetzung mit Angehörigen, Zuweisern und Nachbetreuenden nimmt eine zentrale Bedeutung ein.
Methode: Das Modell einer integrierten, gemeinsam chirurgisch und geriatrisch geprägten Versorgungskette kann die Behandlungsresultate dieser Risikopopulation verbessen. Es zeigen sich im Vergleich zur üblichen Versorgung positive Effekte auf die spitalassoziierten Komplikationen, die Liegezeiten im Spital, die Rehospitalisationen und die Mortalität. Seit September 2012 betreibt das Stadtspital Waid ein „Zentrum für Gerontotraumatologie“, um den speziellen Bedürfnissen dieser Patienten besser gerecht zu werden. Das Zentrum zeichnet sich durch vier wesentliche Merkmale aus: Ein chirurgisch-geriatrisches Co-Management, eine enge Verknüpfung der verschiedenen Disziplinen und Behandlungssektoren, ein klar definierten

Behandlungspfad und die Anwendung von neuesten Erkenntnissen in der operativen Frakturversorgung.

Zusammenfassung: Gerontotraumatologische Patienten haben ein hohes Risiko für Komplikationen im Spitalverlauf. Ihre Bedürfnisse unterscheiden sich stark von denjenigen junger Patienten. Speziell kognitive Einschränkungen, Komorbiditäten und Polypharmazie führen zu Verzögerungen im Heilungsverlauf. Eine integrierte, gemeinsam chirurgisch-geriatrisch getragene Versorgung kann die Behandlungsresultate verbessern. In der Umsetzung stellen sich allerdings zahlreiche Herausforderungen, die mitunter auch ökonomisch begründet sind. Ausgebaute, gut vernetzte hausärztliche, chirurgische und geriatrische Behandlungsstrukturen sind die Basis für eine erfolgreiche Versorgung dieser verletzlichen Patientenpopulation.

FM295 Early detection of gait impairment, fall risk and cognitive decline

Stephanie Bridenbaugh
Basel Mobility Center, Felix Platter-Spital, Universitäres Zentrum für Altersmedizin, Basel, Switzerland

Background: Gait and cognition are closely associated. Older adults with gait deficits have an increased risk of developing cognitive deficits. Cognitive deficits are associated with worsened gait. Both gait and cognitive impairments are risk factors for falls in older adults.
Objectives: (1) To briefly highlight the association between gait and cognition, particularly executive function, (2) to present motor-cognitive dual tasking test paradigms and (3) to provide an algorithm for standardized mobility tests that can quickly and easily be performed in a private practice or on a hospital ward.
Materials and methods: A Pubmed review of current literature on the topic as well as the personal experience and recommendations of the author are presented. Assessments summarized: clock-drawing test, stops walking when talking test, normal walking speed, Timed Up and Go test - regular, as a dual task and imagined. Tests of balance and vestibular functions are also important aspects of mobility assessments however, due to time constraints, cannot be presented here.
Results: The author recommends that at least two of the presented assessments should be performed at each clinical visit in all patients age 65 years or older. If one of the assessments presented provides abnormal results, patients should be referred to a gait specialist for an in-depth quantitative gait analysis.
Conclusions: Assessments of functional mobility, fall risk and cognition should be an integral part of every comprehensive geriatric assessment. Quantitative gait analysis allows not only the early detection of gait deficits and fall risk, but also of cognitive deficits. Early detection allows for timely implementation of targeted interventions to improve gait and/or cognition.

Gastgesellschaft SGH: Presidential Symposium

Société conviée SSH: Presidential Symposium

FM296 Angiogenic markers in plasma cell myeloma patients treated with novel agents

Michael Medinger, Jörg Halter, Andreas Buser, Dominik Heim, Sabine Gerull, Martin Stern, Jakob Passweg
Hämatologie, Universitätsspital Basel, Basel, Switzerland

Background: Angiogenesis plays an important role in the pathogenesis and in progression of plasma cell myeloma (PCM). Novel agents such as thalidomide, lenalidomide and bortezomib, have in part antiangiogenic mechanisms of action. In this study, we examined angiogenic markers in patients with PCM and correlated these markers to treatment response to novel agents.
Patients and methods: We included 93 patients newly diagnosed with PCM treated with novel agents thalidomide or lenalidomide ((immunomodulatory drugs; IMiDs), bortezomib, or a combination of IMiD and bortezomib. A panel of serum angiogenic markers was assessed by a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) before and in the course of the therapy. The response evaluation was performed after three cycles of therapy. The patients were divided into responders [(stringent complete remission (sCR), complette remission (CR), very good partial response (VGPR)] and non-responders [(partial response (PR) stable disease (SD), progressive disease (PD)].
Results: The CR plus VGPR rate was 45% in the IMiD-based group (13/29), 52% in the bortezomib-based group (16/30) and 58% in the combination group (20/34). Baseline levels of vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), tumor necrosis factor-α (TNFα), and angiopoietin-2 (ANG2) correlated positively with advanced disease stage ($p < 0.005$ in each case). Regarding all 93 patients, levels of VEGF, soluble VEGF receptor-2 (sVEGFR2), basic fibroblast growth factor (bFGF), placental-derived growth factor (PGF), ANG2, HGF and neuropilin-1 (NRP1) were significantly different in responders compared to non-responders (Table 1).

	Responders			Non-responders		
	Baseline	After 3 cycles	p-Value	Baseline	After 3 cycles	p-Value
VEGF (pg/ml)	423 ± 123	270 ± 75	<0.005	399 ± 155	449 ± 123	0.15
sVEGFR-2 (pg/ml)	2153 ± 723	4523 ± 871	<0.005	1923 ± 788	2470 ± 688	0.73
bFGF (pg/ml)	8 ± 4	4 ± 2	0.04	9 ± 3	11 ± 5	0.67
PGF (pg/ml)	423 ± 77	301 ± 44	<0.005	510 ± 155	600 ± 99	0.45
ANG2 (pg/ml)	553 ± 158	289 ± 99	<0.005	622 ± 202	570 ± 176	0.34
HGF (pg/ml)	1260 ± 245	723 ± 201	<0.005	1011 ± 155	960 ± 102	0.52
IL6 (pg/ml)	79 ± 17	50 ± 13	<0.005	66 ± 14	33 ± 12	0.03
TNFα (pg/ml)	44 ± 12	37 ± 9	0.07	33 ± 14	40 ± 12	0.06
NRP1 (ng/ml)	320 ± 79	622 ± 99	<0.005	379 ± 82	423 ± 99	0.81

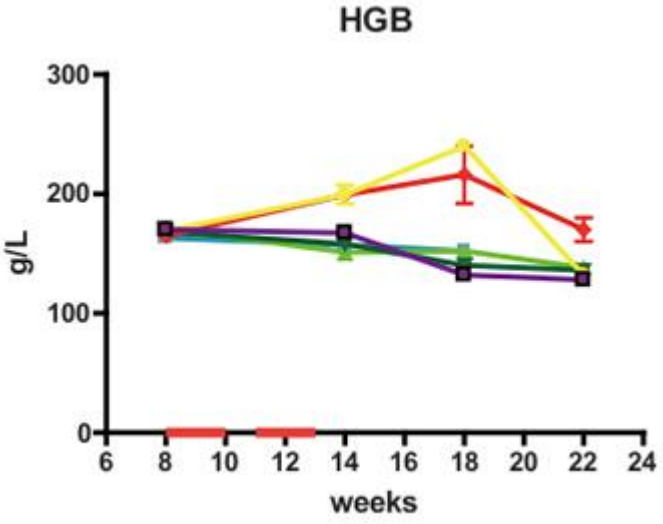
[Table1]

The levels of these angiogenic factors were significantly different in the IMiD-based group and the combination group after therapy but not in the bortezomib group.
Conclusion: The mode of action of IMiDs possibly leads them to have a greater antiangiogenic effect than bortezomib and thus the levels of angiogenic markers was more influenced by IMiD-based therapies in PCM. This study contributes in the understanding of the mode of action of novel agents in the treatment of PCM.

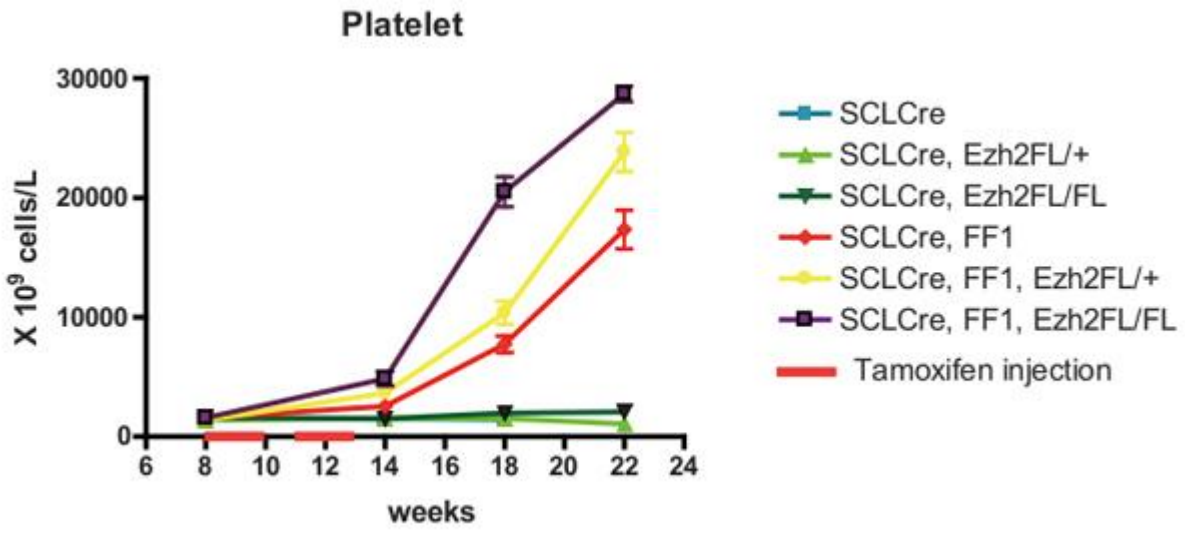
FM297 Jak2V617F and loss of Ezh2 in hematopoietic cells contribute synergistically to myeloproliferative neoplasm initiation potential, and accelerate progression of disease

Takafumi Shimizu[1], Hui Hao-Shen[1], Lucia Kubovcakova[1], Barbara Szczerba[1], Yukiko Shimizu[1], Pontus Lundberg[1], Stephan Dirnhofer[2], Stuart H. Orkin[3], Radek C. Skoda[1]
[1]Experimental Hematology, University Hospital Basel, Dept. of Biomedicine, [2]Pathologie, Universitätsspital Basel, Basel, Switzerland, [3]Dept. of Pediatric Oncology, Harvard Medical School, Boston, MA, United States

Backgroud: JAK2-V617F, is the most common molecular abnormality in myeloproliferative neoplasms (MPNs) and appears in patients with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Ezh2 catalyzes methylation of H3K27, and is frequently mutated in MPN patients. Many JAK2-V617F-positive MPN patients harbor other mutations, but combination effects of JAK2-V617F and Ezh2 mutation have not been analyzed.
Methods and results: To investigate the interaction between the two kinds of mutation in hematopoiesis, we studied transgenic mice with conditional expression of JAK2-V617F, and inducible loss-of-function of Ezh2, both singly and in combination. Conditional expression of Cre was achieved using the SclCre^{ER} system with Tamoxifen injection, leading to excision of loxP-flanked alleles of Ezh2, and simultaneously induced expression of JAK2-V617F (FF1).
Ezh2$^{+/-}$ mice showed no changes in peripheral blood, but Ezh2$^{-/-}$ mice showed slightly increased platelet counts compared to control mice. FF1 mice showed a typical PV signature, including erythrocytosis, thrombocytosis and neutrophilia with mild fibrosis (Grade: 1). FF1;Ezh2$^{+/-}$ mice also showed typical PV with more pronounced thrombocytosis, neutrophilia and more excessive fibrosis (Grade: 1-2) than FF1 mice. FF1;Ezh2$^{-/-}$ mice had even shorter survival and showed more profound thrombocytosis with obvious fibrosis associated with collagen fiber formation and osteosclerosis (Grade: 2) than FF1;Ezh2$^{+/-}$ mice, but without erythrocytosis. FF1 mice showed expansion of hematopoietic stem/progenitor cells in bone marrow and/or spleen, and these expansion were augmented in FF1;Ezh2$^{+/-}$ mice and FF1;Ezh2$^{-/-}$ mice. Notably, megakaryocyte lineage was further expanded in FF1;Ezh2$^{-/-}$ mice. Finally, disease initiation was evaluated by bone marrow transplantations at limiting dilution mixed with competitor cells. Bone marrow cells with FF1;Ezh2$^{+/-}$ also showed stronger reconstitution capacity, and greater disease initiative potential than FF1. Bone marrow cells with Ezh2$^{+/-}$ alone already showed higher reconstitution capacity than WT control.
Summary: We found that heterozygous loss-of-function of Ezh2 accelerated JAK2-V617F-induced MPNs. Especially JAK2-V617F with Ezh2 homozygous loss-of-function induced excessive megakaryopoiesis and resulted in PMF. JAK2-V617F with heterozygous deletion of Ezh2 synergistically enhanced bone marrow reconstitution and disease initiative potential.



[Hemoglobin values]



[Platelet counts]

FM298 **Characterization of single sorted anti-ADAMTS13 specific B cells from the spleen of acquired Thrombotic Thrombocytopenic Purpura (aTTP) patients**

Magdalena Skowronska, Monica Schaller, Johanna Anna Kremer Hovinga
University Clinic of Hematology, Central Hematology Laboratory and Department of Clinical Research, Inselspital, Bern, Switzerland

Introduction: Autoantibodies (Abs) that neutralize and/or accelerate the clearance of ADAMTS13 cause acquired thrombotic thrombocytopenic purpura (aTTP). Since increasing evidence points at the spleen as a major reservoir for antigen specific memory B-cells, we investigated the splenic B-cell population and frequency of ADAMTS13-specific B-cells in the spleen of aTTP patients to better understand the humoral autoimmune response and to develop an autoantibody/B-cells targeted therapy.
Methods: Splenic mononuclear cells of seven aTTP patients (two treated with Rituximab) were analysed by flow cytometry. The frequencies of highly positive anti-ADAMTS13 B-cells among naïve, un-, switched memory B-cells and plasma cells were determined. B-cells bearing anti-ADAMTS13 IgG were individually sorted based on binding to fluorescently labelled rADAMTS13. Gene transcripts of single cells were reverse-transcribed followed by nested PCR to amplify IgG heavy/light chain genes and sequencing. Identifying the Ig variable domains (V) and V-(D)-J junctions i.e. antigen binding region (CDR3) was performed using IMIGT/V-QUEST tool.
Results: Anti-ADAMTS13 cells were detected in the spleen of all patients (average 0.057% of total B-cell population) with highest prevalence among plasma cells. The two Rituximab treated patients had decreased levels of CD19/CD20 positive cells (1% and 20% of lymphocytes after T-cell/monocyte exclusion), compare to Rituximab- naïve (~63%). Splenic anti-ADAMTS13 specific B-cells of four aTTP patients revealed 83 Abs from which we analysed the CDR3 diversity. Most frequently used V-genes were IGHV1-69, IGHV3-30, IGHV5-51 (15%, 12%, 8%) and Abs had average germline identity of 92.2%. Average length of the CDR3 region was 17 amino acids. Igκ light chain was used by 41 Abs and 30 Abs were Igλ (light chain determination failed in 10 clones). We detected two cells bearing Abs which were positive for both light chains: Igκ+, Igλ+.
Conclusion: Specific anti-ADAMTS13 B-cells were found in the spleen of all aTTP patients, in a range similar to ITP patients, including plasma cells known to be unaffected by Rituximab. Currently we clone selected single sorted monoclonal Abs. Functional testing will allow selection of the inhibitory Abs to be used as tools to develop antigen-specific therapies for aTTP.

Gastgesellschaft SGH: Experimental Hematology

Société conviée SSH: Experimental Hematology

FM299 Whole-exome sequencing on a large pedigree of familial acute myeloid leukemia with a 45-year follow-up identifies a novel germ-line C-terminal CEBPA mutation

Katja Seipel[1], Anand Pathak[2], Douglas R. Stewart[2], Beatrice U. Mueller[3], Thomas Pabst[1]
[1]Department für Medizinische Onkologie, Inselspital, Bern, Switzerland, [2]National Cancer Institute, Bethesda, MD, United States, [3]Department für Klinische Forschung, Universität Bern, Bern, Switzerland

Introduction: Familial acute myeloid leukemia (AML) is rare and linked to germ-line mutations in the transcription factors *RUNX1, GATA2* or *CEBPA.* The myeloid key differentiation factor *CEBPA* is an single-exon gene, and conditional *CEBPA* deficient mice develop a myeloblastic AML phenotype. The *CEBPA* protein consists of two N-terminal transactivating domains and the C-terminal basic DNA binding and bZIP leucine-zipper dimerization domains. Previously identified germ-line *CEBPA* mutations were exclusively heterozygous dominant-negative N-terminal frame-shift mutations, with somatic C-terminal *CEBPA* mutations being the most common genomic second-hit event.
Methods: Whole-exome sequencing was conducted on a large pedigree with familial AML first described at the NIH in 1969. A stringent variant filtering was performed against the NCI DCEG CGR database (1170 exomes from families with cancer) and the NHLBI Exome Sequencing Project European-American population.
Results: The sequencing analysis identified a germ-line C-terminal *CEBPA* Q311P single base pair substitution. Unlike previously identified germ-line N-terminal frame-shift *CEBPA* mutations, the Q311P in-frame mutation was located in the C-terminal bZip domain. The Q311P variant was predicted to be deleterious by *in silico* algorithms, and this specific residue was highly conserved among *CEBPA* orthologs and paralogs. Protein structural modeling suggested that the Q311P mutation alters the potential of the *CEBPA* dimer to bind DNA. In fact, we observed that the Q311P mutant *CEBPA* protein had attenuated DNA binding potential in electrophoretic mobility shift assays. Consequently, we found that the Q311P mutation had reduced transactivation potential of a *CEBPA* target gene promoter, consistent with a loss-of-function mutation. Noteworthy, we observed incomplete penetrance (46%) of *CEBPA* Q311P in affected carriers and no other types of cancers or leukemias segregating with the mutation after 45 years of follow-up.
Conclusion: This report describes the identification of a novel *CEBPA* germ-line mutation, and the functional validation of this mutant *CEBPA* variant. We provide an estimate of the penetrance of AML in this extended family. This study reveals that a germ-line mutation in the C-terminal bZip domain can alter the ability of *CEBPA* to bind DNA and reduces its transactivation potential ultimately leading to AML though with lower penetrance compared to the canonical N-terminal frame-shift *CEBPA* germ-line mutations.

FM300 The zebrafish homologue of the murine *Evi1* gene critically regulates HSC development

Martina Konantz[1], Joëlle Müller[1], Anna Lenard[1], Kelli J. Carroll[2], Viginie Esain[2], Trista E. North[2], Claudia Lengerke[1,3]
[1]Department of Biomedicine, University Hospital Basel, Basel, Switzerland, [2]Department of Pathology, Harvard Medical School, BIDMC, Boston, MA, United States, [3]Clinic for Hematology, University Hospital Basel, Basel, Switzerland

Objectives: The *Evi1* locus was originally identified as a common site of retroviral integration in murine myeloid tumors. Several reports associate *Evi1* expression with aggressiveness in myeloid leukemia. Since developmental pathways often reactivate in cancer, we hypothesize that *Evi1* also plays critical roles during developmental hematopoiesis. Here, we employ the zebrafish model to study how *evi1* modulates early blood development.

Methods: Genetic modifications were obtained by injection of inhibitory morpholino oligonucleotides or mRNA in the ZF zygote or with the help of heat-shock inducible transgenic lines. Haematopoiesis was analysed by *in situ* hybridisation for haematopoietic markers and microscopy, live cell imaging and flow cytometry of transgenic lines. TUNEL and pH3 antibody staining were conducted on whole embryos to assess apoptosis or proliferation.
Results: Knockdown of *evi1* strongly impaired the development of *runx1/cmyb*+ HSCs in the AGM. Consistently, *evi1* morphants lacked *ikaros*+ lymphocyte precursor cells and *rag*+ T-lymphocytes and, at later stages, displayed reduced numbers of circulating *globin-gfp* or *lyz-gfp* cells and impaired megakaryopoiesis. To dissect the mechanisms by which *evi1* regulates HSC formation, we analyzed genes specifically expressed in the dorsal aorta (DA), where HSCs emerge from the hemogenic endothelium (HE). We hypothesize that *evi1* regulates HSC specification from the HE, since detailed analyses show reduced aortic expression of *efnb2a* and *dlc*. Live imaging of emerging HSCs using double transgenic *kdrl:mKate-CAAX;cmyb:GFP* embryos support these findings, since we observe less mKate+/GFP+ cells emerge from the ventral wall of the DA in *evi1* morphants. Increased apoptosis and decreased proliferation in the AGM region of our morphants furthermore suggest important additional effects of *evi1* on HSC biology beyond specification. On the molecular level, *evi1* morphants showed reduced levels of *gata2* and *notch* pathway members and HSC formation was rescued by induction of either of the two as well as *vegfa* as a further upstream pathway.
Conclusions: Our data suggest that *evi1* enhances blood stem/progenitor survival and regulates HSC specification from the HE via activation of *notch* and downstream *gata2* pathways. Currently, we analyze the direct molecular interactions mediated by *evi1* during these different regulatory steps and use the CRISPR/Cas9 system to generate *evi1* mutant fish for further validation of our findings.

FM301 Next generation humanized mice support engraftment of myelofibrosis CD34+ cells

Alexandre Theocharides[1], Rouven Mueller[1], Yasuyuki Saito[1,2], Richard A. Flavell[3], Markus G. Manz[1]
[1]Division of Hematology, University Hospital Zurich, Zurich, Switzerland, [2]Division of Molecular and Cellular Signaling, Kobe University Graduate School of Medicine, Kobe, Japan, [3]Immunobiology, Yale University School of Medicine, New Haven, CT, United States

Introduction: Engraftment of CD34+ peripheral blood cells from patients with myelofibrosis (MF) in murine xenograft models is poor (Wang et al., JCI 2012) and is possibly explained by the lack of supportive microenvironmental factors. Thrombopoietin (TPO) has been implicated in the pathogenesis of MF (Schepers et al., Cell Stem Cell 2013, Dadfarnia et al., Blood 2014). Also, the interaction between human hematopoietic cells and SIRPα expressed on mouse macrophages is critical for human engraftment in xenografts (Takenaka et al., Nature Immunology 2007). We hypothesized that the constitutive expression of human TPO and human SIRPα may promote the development of the human MF clone in mouse xenografts.
Methods: Purified peripheral blood CD34+ cells were collected from MF patients and intrahepatically transplanted into sublethally irradiated newborn humanSIRPα-transgenic/humanTPO-knockin Rag2-/-gamma-/- mice (TPO-SIRPα mice). Mice were sacrificed 12-16 weeks after transplantation.
Results: Three out of six samples generated a human graft of ≥20% human CD45+ cells, while the three other samples generated engraftment of 0.1-3%. The human graft was mainly composed of myeloid cells and monocytic differentiation was observed. In 2/2 experiments analysed, a JAK2-V617F and a CALR type 2 mutation were detected in the bone marrow of engrafted mice transplanted with the respective patient sample. Spleen weight was significantly increased in mice engrafted with human MF and was the consequence of increased murine extramedullary hematopoiesis. While neither the DIPSS, nor the presence of myeloid precursors in the peripheral blood (blasts excluded) were predictive of human MF engraftment, the presence of blasts in the peripheral blood significantly correlated with engraftment potential. Importantly, none of the patients developed acute leukemia during follow-up. Finally, preliminary evidence suggests that TPO-SIRPα mice are more supportive of human MF engraftment than NSG mice. **Conclusions:** The presented xenograft model supports robust engraftment of human peripheral blood MF cells and further supports a role for TPO in the pathogenesis of MF. In contrast to previous models TPO-SIRPα mice strongly

promote myeloid rather than lymphoid engraftment. The tight correlation between the presence of peripheral blood blasts and the human MF engraftment potential suggests that human MF stem cells reside in the blast population.

FM302 Induction of MLL-AF9 in hematopoietic stem cell results in highly invasive AML characterized by EMT-related genetic signatures linked to poor overall survival

Vaia Stavropoulou[1], Susanne Kaspar[2], Laurent Brault[1], Mathijs A. Sanders[3], Sabine Juge[1], Alexander Tzankov[4], Michael Kyba[5], Peter J. Valk[3], Antoine H.F.M. Peters[2], Juerg Schwaller[1]
[1]Universitäts-Kinderspital beider Basel, [2]Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland, [3]Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Universitätsspital Basel, Basel, Switzerland, [5]University of Minnesota, Minneapolis, MN, United States

To address the impact of cellular origin on acute myeloid leukemia (AML), we modeled the disease originating from long-term hematopoietic stem cells (LT-HSCs) and more committed myeloid progenitors using inducible "*iMLL-AF9*" transgenic mice. *Ex vivo* immortalized cells displayed several origin-related growth and drug resistance characteristics associated with distinct gene expression signatures. Intriguingly, induction of *iMLL-AF9* in LT-HSCs caused a particularly aggressive AML phenotype in 15% of the mice, characterized by a drastically short latency, high white blood counts, diffuse multi-organ infiltration and chemo-resistance. The aggressive phenotype was associated with expression of genes previously implicated in cell migration, invasion, inflammation and the epithelial-mesenchymal transition (EMT) in solid cancers. shRNA based knock-down experiments demonstrated functional importance of selected candidate genes in cell migration and invasion. Remarkably, cross-species comparative expression profiling regarding origin and aggressiveness identified 111 up-regulated genes with important functions in migration and invasion, including *IL1B*, *IGF1R*, *KDM5B*, *LATS2*, *MAP3K8*, *MMP8*, *S100A8* and *S100A9,* of which 139 out of 193 probe sets were significantly associated with poor overall survival in a larger cohort of AML patients. The aggressive signature was consisted of many known EMT regulators like*TCF4* and characterized about 20% of patients harboring 11q23 alterations, but also all patients harboring 3q26 alterations involving the *EVI1* transcription factor. Our data strongly support the previously disputed theory that human AML may arise from stem and/or oligo-potent progenitors contributing thus to the great heterogeneity of AML reflected by differences in drug resistance and overall survival. Furthermore cross-species comparison of genetic signatures revealed a large number of genes that might serve as biomarkers for stem-cell derived aggressive disease as well as therapeutic targets for more personalized therapeutic interventions.

FM303 Mutational profile of childhood myeloproliferative neoplasms

Ronny Nienhold[1], Axel Karow[1], Pontus Lundberg[1], Edoardo Peroni[2], Maria C. Putti[3], Maria L. Randi[2], Radek C. Skoda[1]
[1]Experimental Hematology, Universityhospital Basel, Department Biomedicine, Basel, Switzerland, [2]University of Padua, Department of Medicine, [3]University of Padua, Department of Pediatric Oncology and Hematology, Padua, Italy

Myeloproliferative neoplasms (MPN) are a group of stem cell disorders predominantly occurring in elderly patients. In children, MPN occur at much lower frequencies. Therefore less is known about the mutational spectrum and the biology of childhood MPN. Lower incidence of JAK2-V617F has been reported in childhood essential thrombocythemia (ET) and polycythemia vera (PV) and in recent studies fewer CALR exon 9 mutations were found in children with ET.
We analyzed the mutational profiles of 22 patients with sporadic pediatric MPN (age ≤18 years at diagnosis) classified as ET (n=19) or PV (n=3). We used a capture based targeted next-generation sequencing (NGS) approach to simultaneously search for mutations in 104 selected genes.
We observed 27 sequence alterations including known driver mutations in JAK2, MPL and CALR. Only

JAK2-V617F and deletions of exon 9 in the CALR gene were recurrent, while all other gene mutations were found only once. Mutations in one of the MPN driver genes JAK2, CALR or MPL were found in a lower percentage of pediatric cases compared to adult MPN patients. Genes involved in epigenetic regulation (TET2, ASXL1, DNMT3A, EZH2, and IDH1), the second most commonly mutated group of genes in adult MPN also showed significantly less mutations in the pediatric cohort. Conversely, a substantial proportion of pediatric MPN patients carried mutations in other genes and a higher percentage of pediatric cases had no detectable mutations in the genes analyzed. This latter group showed a trend towards higher platelet counts compared to patients carrying somatic mutations.
Our study illustrates similarities but also differences in the mutational landscape between pediatric and adult MPN and shows that a larger proportion of pediatric patients have no detectable mutation in any of the genes known to be associated with MPN. Pediatric MPN patients overall also display fewer mutations in genes involved in epigenetic regulation.

FM304 An unexpected role for Ribonuclease Inhibitor (RNH1) in erythropoiesis

Ramanjaneyulu Allam[1,2], Vijaykumar Chennupati[3], Diogo F.T. Veiga[4], Kendle M. Maslowski[2], Aubry Tardivel[2], Manfredo Quadroni[5], Michel A. Duchosal[6], H. Robson MacDonald[3], Nicolas Fasel[2], Anne Angelillo-Scherrer[7], Pascal Schneider[2], Trang Hoang[4]
[1]Department of Clinical Research, Laboratory L613 at 6th floor, University of Bern, Bern, [2]Department of Biochemistry, [3]Ludwig Center for Cancer Research, University of Lausanne, Epalinges, Switzerland, [4]Institute of Research in Immunology and Cancer, University of Montreal, Montréal, QC, Canada, [5]Protein Analysis Facility, University of Lausanne, Epalinges, [6]University Hospital of Lausanne, Service and Central Laboratory of Hematology, CHUV, Lausanne, [7]Universitätsklinik für Hämatologie und Hämatologisches Zentrallabor, Inselspital, University Hospital Bern, Bern, Switzerland

Introduction: Ribonuclease Inhibitor (RNH1) is a ubiquitously expressed leucine-rich repeat protein. RNH1 binds to and inhibits pancreatic type ribonucleases. Further, RNH1 contains numerous cysteine residues whose sulfhydryl groups might play key structural roles and protect from oxidative damage. Despite of all these observations, the role of *RNH1 in vivo* remains unexplored. Here, we describe an essential role for *Rnh1* in the regulation of erythropoiesis by controlling erythroid differentiation.
Methods: *Rnh1*-deficient (*Rnh1*$^{-/-}$) mice were generated by homologous recombination and embryos were analyzed by histopathology, flow cytometry and immuno fluorescence. To understand how Rnh1 regulates erythropoiesis we performed microarrays, mass spectrometry, western blot and polysome analysis.
Results: *Rnh1*$^{-/-}$ embryos die between embryonic days E8.5 to E10 due to severe decrease in erythroid cells. Similar percentages of c-Kit^{+}CD41^{+} cells (Hematopoietic stem/progenitor cells) were present in *Rnh1*$^{-/-}$ yolk sacs compared to control genotypes, however differentiation of mature erythroid cells was impaired. Gene expression studies revealed that levels of hematopoietic transcription factors (TF) in *Rnh1*-deficient yolk sacs were normal, but their target genes were down-regulated. These results indicate that a post-transcriptional mechanism that affects TF gene function. Supporting this, protein levels of the erythroid TFs GATA1 and PPARγ, previously shown to control the proliferation and differentiation of erythroid progenitors, were selectively impaired. However global translation is not affected in *Rnh1*$^{-/-}$ embryos, suggesting that Rnh1 deficiency specifically affects the translation of erythroid transcription factors.
At the molecular level, using the human erythroid K562 cell line, we found that, RNH1 binds to ribosomal proteins and positively regulates the protein translation. *RNH1*-deficiency decreased polysome formation and conversely its overexpression increased polysome formation. Further, RNH1 facilitated polysome formation on GATA1 and PPARγ mRNAs to confer transcript-specific translation. These results suggest that RNH1 regulates erythroid TFs translation.
Conclusion: RNH1 is a novel ribosomal associated protein and its deficiency impairs the translation of erythroid-specific TFs, which leads to arrest in erythroid maturation. Collectively our results unravel the important biological function of *Rnh1* in the regulation of erythropoiesis.

FM305 *CDX2* regulates human leukemic cell clonogenicity and *in vivo* repopulation capacity

Anna Paczulla[1], Matthias Grauer[2], Ursula Kohlhofer[3], Leticia Quintanilla-Martinez[3], Lothar Kanz[2], Claudia Lengerke[1,4]
[1]Department of Biomedicine, University Hospital Basel, Basel, Switzerland, [2]Department of Hematology & Oncology, University of Tuebingen Medical Center II, [3]Department of Pathology, University of Tuebingen, Tuebingen, Germany, [4]Clinic for Hematology, University Hospital Basel, Basel, Switzerland

Objectives: The caudal-type homeobox (*CDX*) gene family has been mainly studied during early development. More recently, *CDX* genes were shown to regulate embryonic hematopoiesis via downstream *HOX* genes and interactions with the *WNT* signaling pathway. Healthy bone marrow (BM) derived hematopoietic cells express low levels of *CDX1* and *CDX4* but lack *CDX2* expression. However, *CDX2* expression is found in >80% of human acute myeloid (AML) and lymphoid leukemia (ALL) and its induction in murine BM cells results in myeloid leukemia. Here, we explore the role of *CDX2* in human healthy hematopoietic and leukemic cells.
Methods: *CDX2* expression was modulated via lentiviral treatment in human BM $CD34^+$ and human leukemic cell lines. To generate cultures displaying a very strong knockdown, individual clones were generated from single transduced cells and analyzed also separately. *CDX2*-modified and control cells were subjected to growth, colony forming (CFU), cell cycle, flow cytometry and qRT-PCR assays and analyzed *in vivo* upon xenotransplantation in NOD/SCID/IL2Rγ^{null} (NSG) mice.
Results: *CDX2* knockdown in leukemic cell lines strongly reduced clonogenic capacity in CFU assays while only slightly reducing growth. Importantly, *CDX2* knockdown leukemic cells transplanted into immunopermissive NSG mice showed profoundly suppressed *in vivo* leukemogenic properties compared to control cells. However, overexpression of *CDX2* in human healthy $CD34^+$ BM derived and also in leukemic cells resulted in a G_0/G_1 cell cycle arrest. In contrast to previous results studied in mice, *CDX2* overexpression alone did not confer *in vivo* leukemogenic properties to healthy human $CD34^+$ cells.
Gene expression analyses of *HOX* and *Wnt*-pathway associated genes revealed modulation of *HOX* gene expression upon *CDX2* modulation. Surprisingly, *CDX2* induction enhanced the expression of the WNT-inhibitory molecule DKK-1 while *CDX2* suppression showed opposite effects. Supplementation of DKK-1 rescued the clonogenicity of *CDX2* knockdown leukemic cells in CFU-assays while, upon application *in vivo*, suppressing healthy hematopoietic stem/progenitor cells.
Conclusion: Our data suggest that *CDX2* regulates *in vivo* leukemogenesis by inducing clonogenic properties in human leukemic cells and that *CDX2* positive leukemic cells may use *DKK-1* expression to fine-tune their Wnt-signaling activity to an optimal dosage that enables leukemia initiation and confers them competitive advantage for bone marrow niche occupation.

Gastgesellschaft SGH: Clinical Hematology

Société conviée SSH: Clinical Hematology

FM306 Low dose ATG for GvHD prophylaxis results in improved survival after allogeneic stem cell transplantation

Laura Binkert[1], Michael Medinger[1], Joerg Halter[1], Dominik Heim[1], Sabine Gerull[1], Andreas Holbro[1], Claudia Lengerke[1], Maja Weisser[2], Jakob Robert Passweg[1]
[1]Hematology Division, [2]Infectious Diseases, University Hospital Basel, Basel, Switzerland

Risks of allogeneic hematopoietic stem cell transplantation (HSCT) include graft-versus-host disease (GvHD), incomplete immune reconstitution and relapse. Graft-versus-leukemia effects are mediated by donor T-lymphocytes. *In vivo* T-cell depletion with antithymocyte globulin (ATG) can attenuate GvHD but increases infection and relapse risk. ATG-Fresenius at a dose of 60mg/kg (20mg/kg on days -3,-2,-1) was standard GvHD prophylaxis in unrelated donor HSCT at our institution. Due to frequent infusion related reaction of the first dose of ATG we changed to an incremental dose regimen (5, 10, 20mg/kg on days -3,-2,-1) and reduced the total dose to 35mg/kg.

265 adults with haematological malignancies, with a first allogeneic HSCT after myeloablative conditioning between 2009 and 2014 were analyzed in this single center cohort study. Patient characteristics are shown in Table 1. Excluded were patients with cord blood (7), haplo-identical (3) or syngeneic grafts (4) and non myeloablative conditionings (59). Groups were compared using the chi squared test for categorical and the Kruskall Wallis test for continuous variables. The Kaplan-Meier estimator and the cumulative incidence function were used where appropriate. Multivariate analyses were done by Cox regression modelling.

Table 1: Patient characteristics

	Control		ATG 35mg/kg		ATG 60mg/kg		p-value
n	145		88		32		
Gender male (n, %)	85	(59)	48	(55)	19	(59)	0.81
Disease (n, %)							0.04
- AML	40	(28)	31	(35)	9	(28)	
- ALL	32	(22)	13	(15)	5	(16)	
- CML	6	(4)	5	(6)	0		
- MDS/MPN	29	(20)	22	(25)	14	(44)	
- Lymphoid Neoplasia	36	(2)	17	(20)	4	(12)	
Disease Stage (n, %)							0.90
- Early	60	(41)	38	(43)	13	(41)	
- Intermediate	46	(32)	30	(34)	9	(28)	
- Advanced	39	(27)	20	(23)	10	(31)	
Donor (n, %)							<0.0001
- Matched related	97	(67)	19	(22)	1	(3)	
- Unrelated	48	(33)	69	(78)	31	(97)	

[Table Baseline]

Outcomes are shown in Table 2. ATG was associated with slower engraftment and less chronic GvHD while no effect was noted on acute grade II-IV GvHD and relapse incidence. Transplant-related-mortality (TRM) was lower and survival higher with low dose ATG. Differences remained after adjustment for significant confounders in the multivariate model where low dose ATG was associated with lower risk of death (RR 0.44, 0.24-0.81; p=0.02), after adjustment for disease stage, patient age and donor type. Other variables, including conditioning, disease, donor-recipient CMV serostatus-, gender- and blood group matching were not associated with survival. ATG was associated with more viral reactivation, viral disease and bacterial blood stream infection, but not invasive fungal infection, and with slower immune reconstitution in particular CD4 counts at day 100.

Table 2: Outcomes

	Control		ATG 35mg/kg		ATG 60mg/kg		p-value
Engraftment, d, median (95% CI)	14	(13 - 15)	18	(17 - 19)	17	(16 - 18)	<0.001
Acute GvHD, % (95% CI)	33	(26 - 42)	30	(21 - 42)	34	(20 - 56)	0.71
Chronic GvHD, % (95% CI)							0.04
- 1 year	55	(46 - 66)	31	(22 - 45)	48	(31 - 73)	
- 2 years	62	(53 - 74)	54	(32 - 89)	57	(40 - 82)	
Relapse, 2 y, % (95% CI)	33	(26 - 42)	27	(18 - 38)	34	(21 - 56)	0.69
TRM, 2 y, % (95% CI)	18	(13 - 26)	8	(4 - 17)	28	(16 - 49)	0.05
Survival, 2 y, % (95% CI)	60	(52 - 68)	75	(64 - 86)	50	(32 - 68)	0.04
CD4, d100, median (95% CI)	0.2	(0.02 - 0.8)	0.09	(0 - 0.5)	0.06	(0.01 - 0.4)	<0.001
Max creatinine d<5, µmol/L, median (95% CI)	73	(36 - 153)	68	(40 - 510)	80	(34 - 169)	<0.05
Max bilirubin d<5, µmol/L, median (95% CI)	13	(4 - 59)	25	(9 - 226)	36	(16 - 90)	<0.001
Blood stream infection, % (95% CI)	12	(8 - 19)	21	(14 - 32)	27	(15 - 48)	0.02
CMV reactivation, % (95% CI)	18	(13 - 26)	35	(27 - 47)	36	(22 - 57)	0.005
EBV reactivation, % (95%CI)	5	(2 - 10)	51	(42 - 63)	66	(51 - 84)	<0.001
Viral infection, % (95% CI)	20	(14 - 28)	29	(20 - 44)	49	(33 - 72)	<0.001

[Table Outcomes]

The recently adopted strategy of using low doses of ATG appears to reduce TRM without increasing relapse, leading to slightly enhanced survival. ATG treatment delays engraftment and increases risks of viral and bacterial infections and has some direct organ toxicity. A controlled trial of ATG use is needed in related donor HSCT.

FM307 Next-generation sequencing based mutation detection and its use for monitoring minimal residual disease and chimerism in patients with acute myeloid leukemia

Pontus Lundberg[1], Heinz Hermann[1], Jakob R. Passweg[2], Dimitrios Tsakiris[1]
[1]Labormedizin, Diagnostische Hämatologie, [2]Klinische Hämatologie, Universitätsspital Basel, Basel, Switzerland

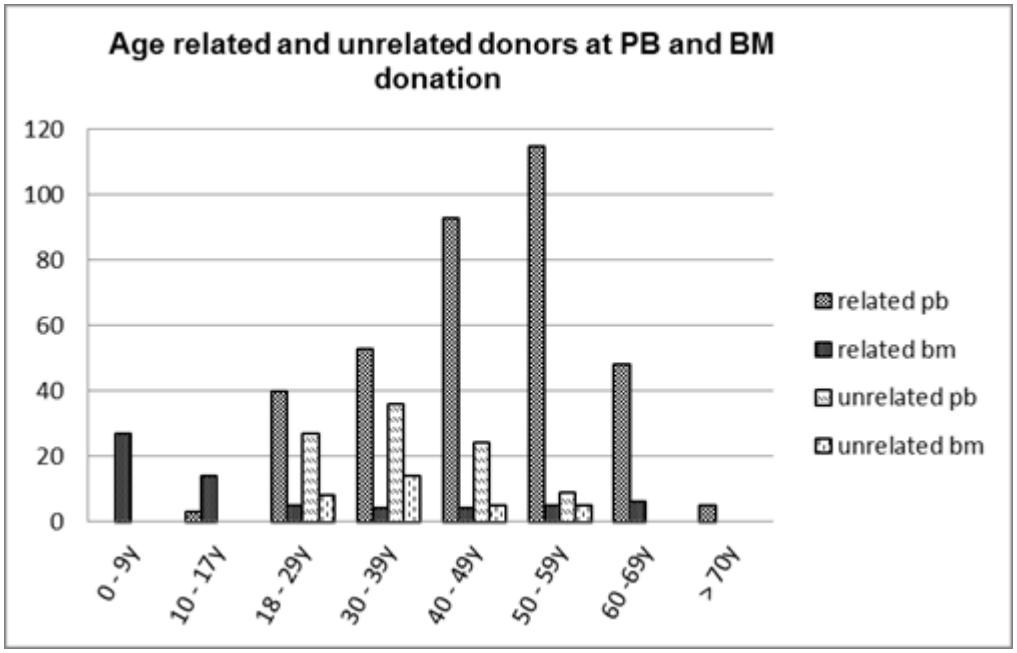
Acute myeloid leukemia (AML) is a heterogeneous disease both clinically as well as genetically. Several next-generation sequencing (NGS) based studies have recently dissected the somatic mutational landscape of AML. Some of the observed mutations have been shown to have important clinical impact, both with regards to patient prognostics and treatment. Another strong prognostic factor for AML is minimal residual disease. Conventional molecular markers such as NPM1 and fusion transcripts can be used to sensitively quantify MRD, but ~50% of AML patients lack molecular targets suitable for MRD monitoring. To address this issue we have developed a NGS based method to screen for mutations that can be used for MRD monitoring, as well as SNPs that can be used to quantify donor/recipient chimerism.
Methods: We have used the commercially available Ion Torrent AML community panel to screen for mutations in the 19 most frequently mutated genes in AML, and complemented this with the human ID panel which genotype for 124 polymorphic SNPs. Patient specific mutations and SNPs were followed during the disease course to assess MRD and chimerism. Furthermore, we performed dilution series where patient DNA was diluted with normal control DNA to assess the limit of sensitivity for MRD and chimerism analyses.
Results: We were able to find somatic mutations in 18/20 (90%) of the screened AML patients. The most frequently observed mutations were in genes previously reported to have a high mutational frequency in AML, such as DNMT3A, TET2 and IDH1/2. In 7/10 patients receiving allogeneic transplantation where patient material were readily available, we were able to track the leukemia clone specific mutations to sensitively monitor MRD. Furthermore, by using at least 3 informative SNPs per donor/recipient pair, we were able to simultaneously assess chimerism. The sensitivity by which the mutations and chimerism were detected by NGS was estimated to be < 0.5% by performing DNA dilution series.
Conclusion: Next-generation sequencing allows detecting mutations that can be used both for the prognostic assessment of AML patients, as well as molecular markers to monitor minimal residual disease in patients lacking conventional molecular markers. This information can be used to evaluate the response of the leukemic clone to treatment and allow for early intervention in case of a detectable molecular relapse.

FM308 Prospective donor outcome follow-up: results and challenges of the first 6 years of Swiss experience

Morven Rüesch[1], Soraya Amar el Dusouqui[2], Eva Buhrfeind[3], Andreas Buser[4], Yves Chalandon[5], Beat M. Frey[6], Tayfun Guengoer[7], Andreas Holbro[4], Saadia Huguet[5], Laura Infanti[4], Gayathri Nair[8], Jakob Passweg[9], Urs Schanz[8], Ulrike Zeilhofer[10], Grazia Nicoloso[3], Joerg Halter[9]
[1]Swiss Blood Stem Cells, Swiss Transfusion SRC (Swiss Red Cross), Berne, [2]Regional Blood Transfusion Service SRC, University Hospital, Geneva, [3]Swiss Blood Stem Cells, Swiss Transfusion SRC, Berne, [4]Regional Blood Transfusion Service, SRC, Basel, [5]Haematology, University Hospital, Geneva, [6]Regional Blood Transfusion Service SRC, Zurich, [7]Division of Stem Cell Transplantation, University Hospital for Children, Zurich, [8]Haematology, University Hospital, Zurich, [9]Haematology, University Hospital, Basel, [10]Haemato-Oncology, University Hospital for Children, Zurich, Switzerland

Introduction: Since 2007, prospective donor outcome follow-up (FU) for unrelated donors (URD) and related donors (RD) has been standardized in Switzerland.
Methods: Since 1.7.2007, data on every haematologic stem cell (HSC) donation performed by URD and RD in CH are collected prospectively in the EBMT database ProMISE. Data collected are donor details, type of collection, number of donations, pre-existing health disorders, complications during / after collection and FU data. Until 30.8.2013 the time-points of data collection were: time of harvest, 1 month (mo), 6mo, 1-5-10 years (y) post donation.
Results: From 1.7. 2007 - 30.6.2013 a total of 578 HSC donations took place in the 4 Swiss collection

centres (CC): 448 by RD and 130 by URD. Of these, 552 were first (424 RD/128 URD), 25 second (23 RD/2 URD) and 1 a third donation (RD). Further analysis includes only first donations: RDs donated 66 bone marrow (BM) and 358 peripheral blood stem cell (PB) products, URDs 32 BM and 96 PB. 54% of the RD and 40% of the URD were female donors. Median age of RD was 8y higher than of URD (47,7y (6mo-74y) vs 39.6y (18-55y)). Age distribution also showed marked differences (fig).



[Age related and unrelated donors at PB and BM dont]

Pre-existing health disorders were more frequent in RD (34%) vs URD (9%). The most frequent were cardiovascular (RD 35% vs URD 25%), haematological (RD 10% vs URD 0) and psychological disorders (RD 10% vs URD 0). No donation-related severe adverse events were reported.

Long-term FU revealed 1 autoimmune disease at 4y (URD), for RD 1 breast malignancy, 1 melanoma and 1 bronchial asthma all at 1y, 1 basal cell carcinoma and 1 case of MGUS at 5y.

After first donation, 89% of RD and 100% of URD had at least one FU during the first year, with large differences between CCs. The transfer of FU management to SBSC in 2012 improved the FU return rate for RD as illustrated in the CC with the previously lowest return rate (table).

	Return rate before transfer	Return rate after transfer
1 mo FU	25%	100%
6 mo FU	44%	77%
1 y FU	50%	73%

[Follow-up return rates]

Conclusion: Donor characteristics differ greatly between RD and URD concerning age and pre-existing health disorders, illustrating the need for RD FU, as FU data from URD are not representative for RD. Donor FU is very good at 1mo for both RD and URD. Collaboration strategies optimizing resources and administration (SBSC/CCs) allow improving the overall FU return rate.

FM309 Chemo- or radiotherapy induced acute myeloid leukemia (t-AML) is not necessarily associated with adverse outcome

Beatrice U. Mueller[1], Corinne Meister[2], Katja Seipel[1], Thomas Pabst[2]
[1]Department of Clinical Research, University of Berne, [2]Department of Medical Oncology, University of Berne and University Hospital, Berne, Switzerland

Background: Therapy related acute myeloid leukemia (t-AML) can occur after exposure to DNA damaging treatment caused by chemo- or radiotherapy for unrelated cancer types with a latency of two to more than ten years. t-AML is commonly considered to be associated with an unfavorable course of the disease since it is frequently characterized by specific cytogenetic abnormalities conferring decreased chemosensitivity and short disease-free (DFS) and overall survival (OS). In the present study, we intended to verify this paradigm.
Methods: In this retrospective analysis, we analyzed all consecutive AML patients diagnosed at the University Hospital in Bern, Switzerland between 01/1990 and 05/2014.
Results: We identified 495 AML patients. 43 (8.7%) patients had t-AML and 452 (91.3%) patients had de novo or AML evolving from MDS/MPD. 30.2% of t-AML had previous chemo-/radiotherapy for hematologic malignancies, 62.8% for solid tumors, and 7% had chemotherapy for rheumatoid diseases. Patients with t-AML had lower leukocyte counts (22.5 versus 37.8 G/L; p = .0138), lower percentage of peripheral blasts (31% versus 44%; p = .0428), and more frequently very-bad risk cytogenetic abnormalities (p < .0001). t-AML tended to be treated more frequently with palliative concepts (23.3% versus 11.7%; p = .0891). For AML patients undergoing intensive induction treatment, no differences in the number of given induction cycles and in the types of consolidation treatment were observed. The complete remission rate after two cycles induction treatment was comparable (65.6% versus 66.8%). After a median follow-up of 24 months (t-AML) and 30 months (all other AML), OS (P = .32) and DFS (P = .36) were not different between the two groups. Furthermore, OS and DFS within the risk categories of good-, intermediate-, bad- and very bad-risk AML patients - defined by cytogenetic and molecular abnormalities - were also not different between t-AML and de novo AML patients.
Conclusion: Our data indicate that patients with AML evolving after previous chemo- and/or radiotherapy for unrelated malignancies have comparable response and survival rates. Treatment algorhythms for t-AML should follow the risk stratification based on molecular and cytogenetic abnormalities as applied for de novo AML patients.

FM310 Anti-torque teno virus immunity in patients undergoing allogeneic hematopoietic stem cell transplantation

Stavroula Masouridi Levrat[1], Amandine Pradier[1], Federico Simonetta[1], Laurent Kaiser[2], Yves Chalandon[1], Eddy Roosnek[1]
[1]Hématologie, [2]Infectious Diseases, Hôpitaux Universitaires de Genève, Geneva, Switzerland

Introduction: Patients (pts) undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are at high risk of infections. Whether immunity at the day of HSCT differs between individual pts is not known. Torque teno virus (TTV) is a small, single stranded DNA *Anellovirus* with >90% prevalence in the population. Infections are latent in immunocompetent individuals but viral loads increase greatly in pts with immunodeficiency. Because TTV is not sensitive to antiviral therapy, it may be an appropriate parameter to measure immunocompetence in pts undergoing HSCT.
Methods: We used TaqMan©-based quantitative PCR to measure TTV titers in 104 adult pts receiving a first allogeneic HSCT for hematological malignancies. Patient groups were compared using non-parametric Mann Whitney test.
Results: At transplant, 28 pts (27%) had high numbers (≥90th percentile of 74 Controls) of viral copies while TTV titers in the others were normal ($TTV^{low/-}$). The latter was most likely evidence of sufficient residual immunity rather than of absence of virus because the number of viral copies in the 58 $TTV^{low/-}$ pts followed during the first months post-transplant, rose sharply between 1 and 2 months. We found no significant impact of the number of chemotherapy cycles received or of time between HSCT and time of diagnosis or of last treatment.
TTV-titers at transplant were strongly associated with the type of disease. Viral copies in the 12 ALL and 9 NHL pts [$67x10^3$ (IQR $0.7x10^3$-$1.57x10^6$) and $218x10^3$ (IQR $15.4x10^3$-$10.3x10^6$) respectively] were significantly higher ($p< 0.0017$;$p< 0.001$) than titers in the 56 AML pts [$0.14x10^3$ (IQR $0.025x10^3$-$3.32x10^3$)] or titers in the 27 pts with other malignancies [$0.16x10^3$ (IQR $0.025x10^3$-$1.16x10^3$)] ($p< 0.0017$;$p< 0.001$). Titers in the 5 Ph^+ ALL pts [$2.0x10^6$ (IQR $112.4x10^3$-$38.5x10^6$)] were significantly higher ($p< 0.018$) than in their 7 Ph^- counterparts [$1.0x10^3$ (IQR $0.1x10^3$-$113.8x10^3$)].
Most ALL/NHL pts had received long-term prednisone and NHL pts had received autologous HSCT while

Ph^+ ALL pts had been treated with tyrosine kinase inhibitors. However, none of the non ALL/NHL pts that had received autologous HSCT (15), long-term-prednisone (11) or tyrosine kinase inhibitors (8) had high TTV-titers.
Conclusion: Titers at HSCT are associated with the type of disease rather than with previously received therapies. TTV titers increase greatly in pts after HSCT and may therefore be a candidate test to quantify immunity.

FM311 Impact of T-cell depletion techniques on post transplant graft versus host disease after allogeneic HSCT with myeloablative conditionning

Anne Pascale Grandjean, Federico Simonetta, Stavroula Masouridi-Levrat, Yordanka Tirefort, Marc Ansari, Yan Beauverd, Audrey Simon, Carole Dantin, Eddy Roosnek, Yves Chalandon
Hopitaux Universitaire de Genève, Genève, Switzerland

Introduction: Because GvHD is a major cause of morbidity and mortality in alloHSCT, different strategies are developed to reduce it´s incidence. T-cell depletion (TCD) using *in vivo* ATG or/and *in vitro* alemtuzumab represent potential strategies. In this study we evaluated the incidence of GvHD using TCD in the bag with or without ATG as compared to non-Tcell depleted alloHSCT.
Materials (or patients) and methods: We performed a retrospective study on 256 patients transplanted from 1997 to 2013 with an alloHSCT from identical siblings or HLA 10/10 matched unrelated donors after MAC. Median patients age was 41 years, median EBMT score 2. 109 patients received partial TCD (pTCD) grafts, consisting of *in vitro* alemtuzumab incubation before infusion followed on day +1 by an add-back of donor T CD3+ cells. 34 patients received *in vivo* ATG administration. 69 patients had combined ATG and pTCD. 44 patients had no TCD. Log-rank Mantel-Cox test was used to compare the 1-year cumulative incidence of grade 2-4 acute GvHD (aGvHD) and 1- and 5-year cumulative incidence of chronic GvHD (cGvHD) and 5-year transplant related mortality (TRM), relapse rate (RR) and overall survival (OS) in patients receiving pTCD alloHSCT with or without ATG, with those receiving non-TCD alloHCST.
Results: Median follow up was 52 months. Grade 2-4 aGvHD 1-year cumulative incidence was decreased in patients receiving pTCD grafts combined with ATG (11%; $p< 0.0001$) compared to patients receiving non-pTCD alloHSCT (58%). No effect of pTCD (37%, $p=0.0537$) grafts or ATG treatment alone (53%, $p=0.9172$) was observed on acute grade 2-4 GvHD incidence. No effect on 1-year and 5-year cumulative incidence of cGvHD was observed for either ATG (15%, $p=0.1132$ and 15%, $p= 0.0902$ respectively) or pTCD alone (27%, $p=0.2631$ and 28%, $p= 0.1942$) compared to non-pTCD (40 % and 44%). We observed a reduction in 1-year and 5-year cumulative incidence cGvHD in patients receiving ATG combined with pTCD (11%, $p=0.001$ and 11%, $p=0.0004$). 5-year TRM and RR were not different between groups. 5-year OS was found worse with ATG alone (33%, $p=0.0061$) with no difference with ATG and pTCD and pTCD alone compared to non-TCD.
Conclusion: pTCD combined with ATG appears to decrease the incidence of acute and cGvHD in patients receiving alloHCST with a MAC from sibling or HLA 10/10 matched unrelated donors without affecting 5-year TRM, RR or OS. These results extend our knowledge of effect of TCD on TRM.

FM312 Divergent socioeconomic consequences of consolidation treatment modalities in AML patients

Beatrice U. Mueller[1], Sandra Stiffler[2], Katja Seipel[1], Thomas Pabst[2]
[1]Department of Clinical Research, University of Berne, [2]Department of Medical Oncology, University of Berne and University Hospital, Berne, Switzerland

Background: Two cycles of induction chemotherapy and subsequent consolidation treatment are a curative concept in 40-45% of acute myeloid leukemia patients. However, the impact of the various consolidation treatment modalities on the duration until resuming professional activities and on the maximum degree of

employment in Swiss AML patients is unknown.
Methods: In this retrospective single-centre analysis, we analyzed all consecutive AML patients diagnosed at an academic institution between 01/1975 and 12/2012 who received two cycles of induction chemotherapy with subsequent consolidation treatment. We focused exclusively on AML patients who never relapsed and who were free of relapse for at least two years at last follow-up. Patients needed to be not older than 62 years at diagnosis. A comprehensive standardized questionnaire was used.
Results: With a questionnaire return rate of 95.5%, 120 AML patients in ongoing first complete remission were evaluable. The median age at diagnosis was 54 years. Consolidation treatment was chemotherapy (CT) in 52 pts (43.3%), autologous transplant (auto-HSCT) in 44 pts (36.7%), and allogeneic transplant (allo-HSCT) in 24 pts (20.0%). 76 pts (63.4%) resumed their previous professional activities, 34 pts (28.3%) never worked again, and 10 pts (8.3%) switched to another professional activity. We found that patients after auto-HSCT or CT resumed their professional activities earlier (5 and 7.5 months, respectively) compared to patients after allo-HSCT (10.0 months; p = .01). The initial median occupational percentage at restart of professional activity was not different (42%, 51%, and 37%, respectively). Patients reached their maximum professional activity (76%, 79%, and 60%; p = .021) earlier after auto-HSCT (9 months) and CT (8.8 months) than after allo-HSCT (15.7 months; p = .003). Patients regained their subjective maximum physical potential (82%, 85%, and 69%, respectively;
p = .006) earlier after auto-HSCT (15.7 months) or CT (14.4 months) than after allo-HSCT
(27.1 months; p = .003).
Conclusion: Our data suggest that the three modalities of consolidation treatment for AML patients in first remission are associated with significantly divergent socioeconomic consequences with regards to restart and percentage of professional activity as well as the ultimate maximum occupational and subjective activity. This information should be integrated in advising AML patients on the various consolidation options.

Gastgesellschaft SGH: Hemostasis, Vascular Biology and Transfusion Medicine

Société conviée SSH: Hemostasis, Vascular Biology and Transfusion Medicine

FM313 Targeting Protein S: a new strategy to treat Hemophilia

Luca Bologna[1,2], Sara Calzavarini[1,2], Raja Prince[1,2], Natacha Dewarrat[1,2], Anne Angelillo-Scherrer[1,2]
[1]University Clinic of Hematology and Central Hematology Laboratory, University Hospital and the University of Bern, [2]Department of Clinical Research, University of Bern, Bern, Switzerland

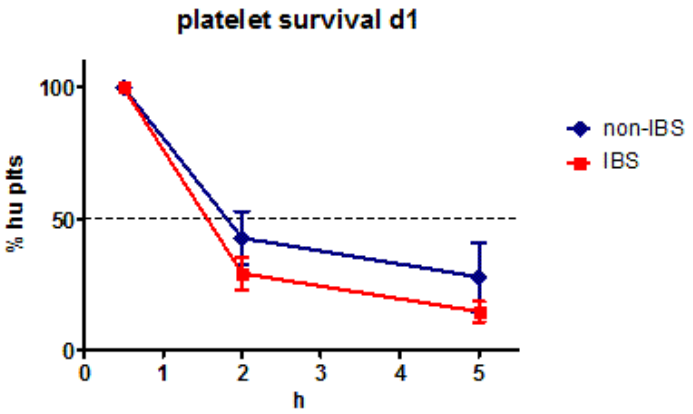
Introduction*:* Hemophilia is an hereditary X-linked disorder characterized by excessive bleeding caused by genetic deficiency of coagulation factors, FVIII for Hemophilia A (HA), FIX for Hemophilia B (HB). Replacement therapy is the mainstay treatment but inhibitory alloantibodies developed against the recombinant products limit cure. Protein S (PS) is an anticoagulant that limits thrombin generation, acting as a cofactor of Activated Protein C and tissue factor pathway inhibitor. Homozygous PS deficiency leads to disseminated intravascular coagulation (DIC) meanwhile heterozygous PS deficiency increases risk of thromboembolic events. Mouse model lacking PS recapitulates aspect of the disease, with $PS^{-/-}$ dying *in utero* due to consumptive coagulopathy. In Hemophilia thrombin generation is reduced, specific blocking of PS might boost FXa generation, thus compensating FVIII or FIX deficiency.
Methods*:* Matings of hemophilic PS heterozygous mice were set to generate HA-$PS^{-/-}$ and HB-$PS^{-/-}$. Mice were investigated for possible overt DIC, and were *in vivo* challenged in venous thrombosis (VTE), tail clipping (TC) and an acute hemarthrosis (AH) models.
Results: HA and HB rescued the lethal $PS^{-/-}$ embryonic phenotype: HA-$PS^{-/-}$ and HB-$PS^{-/-}$ pups were found alive at the expected Mendelian frequency (80/366, 22% and 17/94, 18% respectively) and showed normal development. These mice had undetectable plasma coagulant FVIII or FIX and antigenic PS levels. Investigation on blood parameters did not show any relevant DIC signs: platelets number, PT, TAT and fibrinogen levels were normal and comparable to HA/HB mice. Once tested in a TF driven VTE, HA $PS^{-/-}$

did not show an increased mortality compared to HA mice (n=15, 88% and n=19, 100% respectively). To evaluate the potential of PS in HA therapy, TC and AH models were investigated. In the TC, HA-PS$^{-/-}$ mice bled less (158±11uL n=6) compared to HA and HA-PS$^{+/-}$ (247±19uL, n=10 and 239±11uL, n=8 respectively, P< 0.006). In the AH, joint swelling of HA-PS$^{-/-}$ mice was also less prominent at 24h (0.02±0.01*vs* 0.88±0.31 in HA, n=5 P=0.01) remaining stable in the following two days (0.02±0.07*vs* 0.59±0.14 in HA, n=5 P=0.006 at 72h).
Conclusion: Lack of PS in mice significantly reduced bleeding in HA without inducing DIC or enhancing thrombotic risk, while limiting swelling in acute hemarthrosis. Further studies on HB mice are ongoing but these preclinical data showed that PS targeting might be a new valuable strategy for hemophilia therapy.

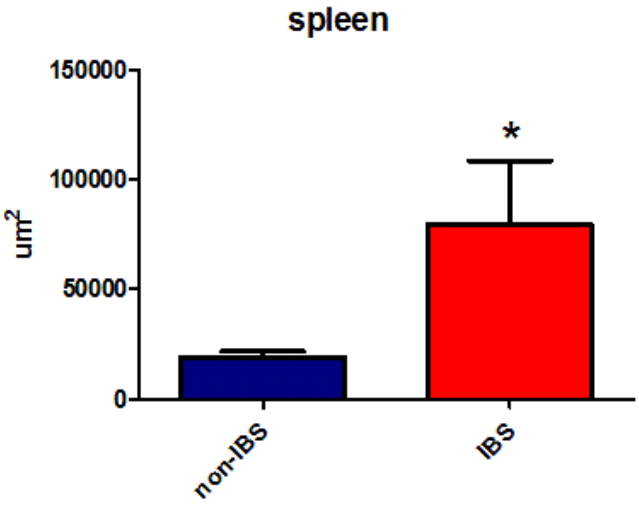
FM314 The intercept blood system: effects on platelet function, apoptosis and survival

Simona Stivala[1], Sara Gobbato[1], Martin F. Reiner[1], Thomas F. Lüscher[2], Sara C. Meyer[3], Laura Infanti[3], Andreas Buser[3], Jürg H. Beer[1,4]
[1]Laboratory for Platelet Research, Center for Molecular Cardiology, Schlieren, [2]Cardiology, University Hospital Zurich, Zurich, [3]Transfusion Center of the Swiss Red Cross, University Hospital Basel, Basel, [4]Internal Medicine, Kantonsspital Baden, Baden, Switzerland

Introduction: The Intercept Blood System (IBS) is currently used worldwide and mandatory in Switzerland to reduce the risk of transfusion-transmitted disease from platelet concentrates (PC). Several trials have shown a reduced count increment (CI) in patients receiving Intercept-treated PC compared to untreated PC, although not an increased risk in major bleeding. This study was undertaken in order to analyze the effect of the IBS on platelet function, assessed *in vitro*, and platelet *in vivo* survival, and to understand the possible underlying mechanisms.
Methods: Platelet apheresis units (AU) were collected from healthy donors and kept untreated (nI) or treated with the IBS following standard blood banking procedures. AUs were kept at 22±2°C under gentle agitation, and samples were taken at d2, 5, and 7 after donation for analysis.
Results: Platelet aggregation was reduced already at d2 in the IBS samples compared to the nI ones (AUC for collagen: 70.71 nI vs 17.37 IBS; AUC for thrombin: 215 nI vs 116.6 IBS, n=13). Platelet GpIb was significantly reduced at d7 in the IBS samples, and P-selectin was increased (GpIb MFI: 2397 nI vs 1853 IBS, p=0.03; P-selectin % +ve: 2.5 nI vs 8.33 IBS). Platelet aggregation to collagen and vWF under low - and high -shear conditions was also reduced upon IBS treatment already at d2 (AUC: 400867 nI vs 205374 IBS, p=0.09). In vivo survival was monitored by injection of fluorescently-labeled platelet into NOD-SCID mice and flow cytometric analysis of small blood samples over time. Platelets from IBS samples showed a faster clearance from the circulation compared to nI platelets (% hu plt at 2h: 42.8% nI vs 29.3% IBS; 5h: 27.9% nI vs 14.9% IBS; n=6). Platelet-positive area was significantly higher in spleen from mice injected with IBS platelets (19083 um^2 nI vs 79395 IBS, n=3, p=0.029). Analysis of the pro- and anti-apoptotic proteins Bak and Bcl-xL by WB and immunofluorescence staining showed a significant increase of Bak in platelets from IBS samples, while Bcl-xL was unchanged (Bak/GAPDH I.I.: 0.08 nI vs 0.12 IBS, n=5/6, p=0.007).
Conclusions: The IBS reduces platelet aggregation to physiologic agonists and *in vivo* platelet survival by inducing platelet apoptosis, thus promoting platelet clearance. The involvement of several intracellular mediators is currently under study in order to test the feasibility of using specific inhibitors to prevent the damage induced by the IBS.



[In vivo patelet survival]



[Platelet in spleen of mice]

FM315 Generation of procoagulant COAT platelets in stored platelet-concentrate units derived from buffy-coat preparations

Debora Bertaggia Calderara[1], David Crettaz[2], Stefano Barelli[1,2], Jean-Daniel Tissot[2], Niels Lion[2], Michel Prudent[2], Lorenzo Alberio[1]
[1]Service et Laboratoire Central d'Hématologie, CHUV, Lausanne, [2]Transfusion Interrégionale CRS, Epalinges, Switzerland

Background: COAT platelets, generated by dual agonist stimulation with collagen and thrombin, are very efficient in sustaining thrombin generation at the site of vessel wall injury. There is evidence that higher amounts of COAT platelets are associated with stroke, while a decreased ability to generate COAT platelets is associated with bleeding diathesis.
Platelet concentrates (PC) can be obtained from the buffy-coat of whole blood donations, or directly by aphaeresis technique. The aim of this work was to investigate various aspects of platelet function, in particular the ability to generate COAT platelets in PC from random donors prepared with the buffy-coat method (BC-PC). In addition we investigated whether the level of COAT platelets in BC-PC was modified either by pathogen inactivation process treatment (Intercept) and/or by prolonged storage of PC units.
Methods: Platelets from BC-PC were analyzed by flow cytometry before pathogen inactivation and during storage extended to 10 days. Two BC-PC from 5 donors each were pooled and split in two bags, one of them was pathogen inactivated by Intercept process (overnight between day 1 and 2) and the other one was left untreated. Flow cytometric analyses were performed immediately after BC-PC preparation (day 1) and

thereafter at days 2, 3, 7, 10 in treated and untreated BC-PC. We measured the efficiency of BC-PC to generate COAT platelets following simultaneous stimulation with thrombin and convulxin, a specific receptor for the collagen receptor GPVI.
Results: Preliminary data show that preparation of BC-PC results in a significant decrease of COAT platelets (with a relative loss up to 80%) compared to platelets in platelet-rich plasma. While in untreated BC-PC the decrease of COAT platelets is constant over time, in Intercept-treated BC-PC the COAT platelet loss appears to progress during storage and is almost complete at day 10.
Conclusion: Preparation of platelet concentrates from buffy-coats seems to decrease the ability to generate procoagulant COAT platelets. Pathogen inactivation by Intercept treatment appears to further impair the formation of COAT platelets. The clinical relevance of this observation is unknown. Current work aims at confirming and identifying the mechanisms underlying this phenomenon.

FM316 Towards better molecular understanding of Protein S deficiency induced purpura fulminans

Raja Prince
Department of Clinical Research, University of Bern, Bern, Switzerland

Introduction: Complete Protein S (PS) deficiency induces lethal skin necrosis and disseminated intravascular coagulation known as Purpura Fulminans (PF). Current knowledge on the molecular basis of PF is uncertain although the imbalance between pro/anticoagulant factors is thought to be the etiological factor. However in the last years, our knowledge on PS has increased, indicating that beyond its role in blood coagulation, it has also cellular functions through the tyrosine kinase receptors (TAM). To elucidate PF pathophysiology, we decided to generate different PF models in vivo in mice. Interestingly, PS shares 44% similarity with the growth arrest specific gene 6 (Gas6). Gas6 exerts cellular functions by binding TAM but Gas6-/- mice showed antithrombotic phenotype in strong contrast to ProS-/-.
Methods and results: To mimic severe PS deficiency in adult mice and monitor the PF development, an inducible ProS gene silencing system (polyI:C- inducible Mx1-Cre) was inserted in both wt and ProSlox/- models (ProSlox/loxMx1Cre+, ProSlox/-Mx1Cre+). Ten days after polyI:C treatment, PS levels was significantly reduced: 47.7±6% in Proslox/loxMx1Cre+ and 14.5±7% in Proslox/-Mx1Cre+. Although the very low PS levels, no skin lesions compatible with PF were observed in 2 months observation period. To deeply reduce PS levels, we administer 0.8mg/day warfarin (vitamin K antagonist) to ProS+/- mice. Early lesions were erythematous with highly visible ear skin vessels, vascular engorgement, intradermal edema and rare intravascular-thrombosis. In advanced lesions we noticed a massive red blood cell extravasation, intra-epidermal hemorrhagic blisters and necrotic areas. To evaluate the potential vasculature defects, ProS-/- embryonic dorsal skin immunostainings were performed. Data showed areas with underdeveloped vascular network and increased RBC extravasation in ProS-/- as compared to wt. Because adult Gas6-/- mice are protected against thrombosis, a mouse model combining PS and Gas6 deficiency was generated. Gas6 deficiency did not rescue ProS-/-. Surprisingly, the mortality rate of ProS-/-Gas6-/- embryos was higher as compare to ProS-/- (27% vs 9% respectively).
Conclusion: During PF development the thrombotic process might be less central than currently admitted. A prominent involvement of vascular wall in PF lesions is observed in ProS-/-. Experiments are ongoing to evaluate if both PS/Gas6-dependent TAM signaling have a role in the permeability of vascular endothelium.

FM317 Predictors of anticoagulation quality in 15'834 patients performing patient self-management of oral anticoagulation with vitamin K antagonists in real-life practice: a survey of the International Self-Monitoring Association of Oral Anticoagulated Patients

Michael Nagler[1,2], Christian Schaefer[3], Walter A. Wuillemin[4,5]
[1]Abteilung Hämatologie und Hämatologisches Zentrallabor, Luzerner Kantonsspital, Luzern, Switzerland, [2]Laboratory of Clinical Thrombosis and Haemostasis, and Cardiovascular Research Institute, Maastricht University Medical Center, Maastricht, The Netherlands, [3]International Self-Montioring Association of Oral Anticoagulated Patients (ISMAAP), Geneva, [4]Division of Haematology and Central Haematology Laboratory, Luzerner Kantonsspital, Luzern, [5]University of Bern, Berne, Switzerland

Background: Patient self-management (PSM) of oral anticoagulation with vitamin K antagonists (VKA) is recommended for patients requiring long-term anticoagulation but some aspects are still under debate. It is not known how to identify patients with a low chance of performing well.
Methods: Data from a large survey of the International Self-Monitoring Association of Orally Anticoagulated Patients (ISMAAP) were used. The percentage of INR values within therapeutic range (TIR) were calculated as outcome variable, and various characteristics were obtained as potential predictors. Logistic regression for low anticoagulation control (TIR below 80% [TIR< 80]) was used. A prediction model was fitted by comparing receiver-operating characteristics (ROC curves).
Results: Questionnaires were completed by 15'834 adult patients (35.2% of distributed), corresponding to an observation period of 148'317 patient-years (median 10 years; IQR 6 to 14 years). Median age was 72 years (IQR 65 to 77 years), 30.1% were female. Indications for anticoagulation were: mechanical heart valve (46.5%), atrial fibrillation (34.3%), venous thromboembolism (16.4%) and others (2.9%). The median TIR was 88.5% (IQR 76.9 to 96.2%). The following variables were related to a higher risk of TIR< 80: higher intensity of therapeutic range (odds ratio [OR] on every level 1.9; 95% CI 1.8 to 2.0), long intervals of measurements (OR > bi-weekly; 1.6; 95% CI 1.4 to 1.8), female sex (OR 1.2; 95% CI 1.1 to 1.3), management other than PSM (OR 1.4; 95% CI 1.3 to 1.6), indication (OR for mechanical heart valve/ venous thromboembolism versus atrial fibrillation/ others 1.4; 95% CI 1.3 to 1.5), higher weekly dosage (OR on every level 1.04; 95% CI 1.02 to 1.06), and employed (OR versus retired 1.0; 0.9, 1.1). No relevant association were found for duration of PSM. The final prediction model for TIR< 80 included the variables intensity of therapeutic range, interval of measurements, type of management, and sex ($p < 0.0001$; likelihood ratio [X^2]: 633.5; area under ROC curve: 0.640). The sensitivity of the prediction model with a threshold of 0.3 was 72.2% (95%CI 70.8, 73.5), specifity was 48.2% (47.1, 49.3).
Conclusion: Using the proposed prediction model, physicians will be able to identify patients with a low chance of performing well, considering additional teaching lessons, regular follow-up, or adjustment of therapeutic ranges. Intensifying support in this patient group will improve care in PSM patients.

FM318 Standardization of thrombin generation assay: testing a new factor XII inhibitor

Sara Calzavarini[1], Claudia Quarroz[1], Vanessa Baeriswyl[2], Christian Heinis[2], Anne Angelillo-Scherrer[1]
[1]University Clinic of Hematology and Central Hematology Laboratory Bern, Bern, [2]Laboratory of Therapeutic Proteins and Peptides, EPFL, Lausanne, Switzerland

Background: Thrombin generation (THG) by means of the calibrated automated thrombogram is a sensitive test for overall assessment of the clotting potential. Despite its common use in research labs, standardization of pre-analytic conditions is lacking preventing its use as clinical diagnostic test. A major drawback is the contact phase activation during blood collection and plasma processing. It has been proposed the addition of corn trypsin inhibitor (CTI) to reduce the FXII activation. However, due to the high cost of CTI and the limited investigations on its effects on TGA induced by different triggers, its use is still very limited. Recently, we developed a new synthetic peptide (FXII618) that in vitro inhibits activated FXII (FXIIa) with high potency and selectivity (Ki = 22 nM; >2000-fold selectivity) than CTI.
Results: To evaluate the effectiveness of FXII618 in the FXII-inhibition in THG assays, we used ellagic acid

(EA) as thrombin trigger in normal plasma treated with increasing FXII618 concentrations. FXII618 reduced the EA-induced THG in a dose-dependent manner, reaching a complete inhibition of thrombin formation already at 20 µg/mL FXII618 (>90% reduction of endogenous thrombin potential (ETP) and peak). In comparison, around 100 µg/mL CTI was needed to reduce thrombin generation to background levels (~ 90% reduction of ETP and > 96% of peak). As the contact activation could induce THG in the absence of an extrinsic- or intrinsic-specific trigger, we evaluate the TGH in not triggered plasma treated with/without FXII618 and CTI. FXII618 inhibited TGH significantly stronger than CTI (lag time: 55.8 ± 3.7 and 38.7 ± 1.9 min, and peak: 60.3 ± 0.8 and 78.0 ± 6.8, nM, respectively).The addition of FXII618 to whole blood soon after collection instead of on processed plasma completely block thrombin activation during 120 minutes of observation period. Both FXII618 and CTI did not affect the TGA, once induced by high levels of TF, thus confirming their specificity for FXII. In low-TF THG, FXII618 reduced the ETP to a similar extent as CTI, but delayed the lag time more potently (lag time: 12.3 ± 0.3 and 8.0 ± 0.2 min, respectively).
Conclusions: The improved blockade of contact activation and the lower manufacturing costs than CTI, make FXII618 an attractive reagent for THG. Additional experiments using pathologic plasma samples are on going in order to validate the use of FXII618 in THG.

Posters

Beste 10 Poster

10 meilleurs posters

P319 "HOSPITAL" score predicts patients at high risk of potentially avoidable readmission: multicenter validation study in Switzerland

Jacques Donzé[1,2,3], Jérôme Stirnemann[4], Pedro Marques-Vidal[5], Drahomir Aujesky[1]
[1]Universitätsklinik für Allgemeine Innere Medizin, Inselspital, Bern University Hospital, Bern, Switzerland, [2]Brigham and Women's Hospital, [3]Harvard Medical School, Boston, MA, United States, [4]Service de Médecine Interne Générale, Hôpitaux Universitaires de Genève, Genève, [5]Département de Médecine Interne, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Background: To improve transition of care, hospitals need to target discharge interventions at patients at high risk of avoidable readmission. The "HOSPITAL" score, derived previously in the US, is an easy to use prediction model that accurately identify those medical patients at high risk of potentially avoidable readmission. It includes the following predictors: Hemoglobin, discharge from an Oncology service, Sodium level, Procedure during the index admission, Index Type of admission (urgent), number of Admission during the last 12 months and Length of stay. In order to test its generalizability in Switzerland, we aimed to externally validate the "HOSPITAL" score in a multicenter study.
Methods: We applied the score to 43,058 adult patients consecutively discharged alive from the medical departments of 3 tertiary care hospitals in Switzerland between January 2011 and December, 2012. The outcome was any potentially avoidable 30-day readmission according to the validated SQLape algorithm. Because the length of stay in Switzerland is longer as in the US, we tailored the categorization of this variable to the median length of stay in Switzerland.
Results: Among all discharged patients, 12.3% (n=5,309) had a 30-day readmission, and 5.2% (n=2,219) a 30-day readmission deemed potentially avoidable. Median length of stay was 6.6 days (IQR 3-12). The discriminatory power of the "HOSPITAL" score to predict potentially avoidable readmission was fair with a C-statistic of 0.67 (95% CI 0.66-0.68). As in the derivation study, patients were classified into 3 risk categories: low (62%), intermediate (25%), and high risk (13%). The estimated proportions of potentially avoidable readmission for each risk category matched the observed proportion: 4.0% vs. 3.9% in low risk patients, 6.7% vs. 7.4% in intermediate risk patients, and 11.1% vs. 10.4% in high risk patients. Among the low risk patients, only 3.5% had a 30-day potentially avoidable readmission. In comparison, 9.7% of the high risk patients had a 30-day potentially avoidable readmission.
Conclusions: The "HOSPITAL" score identified patients at high risk of 30-day potentially avoidable readmission with fair discrimination when applied to a large multicenter cohort of medical patients in Switzerland. The "HOSPITAL" score has the potential to easily identify patients in need of more intensive transitional care interventions.

P320 Prescription of hypnotics during hospital stay: an epidemiological study in a Swiss hospital

Laurence Schumacher[1], Anne-Laure Blanc[1], Damien Tagan[2], Annelore Sautebin[2], Nicolas Widmer[1]
[1]Pharmacie des Hôpitaux de l'Est Lémanique (PHEL), [2]Hôpital Riviera-Chablais (HRC), Vevey, Switzerland

Background and objective: Hypnotics have been associated with many adverse effects, such as drowsiness, confusion, falls and dizziness, especially in elderly population. Moreover, chronic use can cause decreased cognitive performance and addiction. A regional prevention campaign "Hypnotic? Not necessarily needed"

conducted in the Canton of Vaud, focused on this topic. This study aims to describe introduction and discharge prescription of hypnotic drugs during stay in an internal medicine ward.
Method: The study took place in a 70 bed internal medicine department of a Swiss regional hospital for a period of 3 months. Inclusion criteria were: age 18 or more, hospital stay for more than 24 hours, discernment and patient's approval. Demographic data (age, gender, diagnosis, co-morbidity) and medication data (chronic hypnotic use, hypnotic's introduction, day of introduction, drug-related problems, and administrative data) were collected.
Results: 290 patients were included. 73% of them were over 65 years old and 58% were women. 34% had a chronic use of hypnotics before hospital stay and 44% had a prescription for hypnotics after hospital stay. Hypnotics medication were introduced in 37% (n=108) of patients, mostly as required (68%). Half (52%) of hypnotics were prescribed during the first 24 hours of hospital stay and 76% of these introductions were not reassessed during hospital stay. Drugs introduced were: benzodiazepines (47%), clomethiazol (32%), benzodiazepine related drugs (11%; zolpidem, zopiclone) and other hypnotics (10%; herbal drugs, melatonin, antidepressant and antipsychotic). Different hypnotics were used depending on age: lorazepam for people < 65 years old, and clomethiazol for ≥ 65 years old. Drug-drug interactions were detected in 68% of new hypnotic prescription: 87% pharmacodynamic (mutual increase of adverse reactions) and 13% pharmacokinetic (impact on drug disposition). After hospital stay, 37% (n=40) of the patients had a new hypnotic drugs on their discharge prescription compared to their preadmission treatment.
Conclusion: Introduction of a hypnotic medication happened in nearly 40% of hospitalized patients. Most of the time, physicians reassessed the new hypnotic on discharges prescriptions, one-third of hypnotics are kept at the end of the hospital stay. These prescriptions may generate chronic use and expose patients to drug-related problem (adverse effects and interactions).
Disclosure of Interest: None
Ethical approval: Yes

P321 Impact of hyponatremia correction on the risk of 30-day readmission and death in patients with congestive heart failure

Jacques D. Donzé[1,2,3], Patrick E. Beeler[2,4], David W W. Bates[2,3]
[1]Bern University Hospital, Bern, Switzerland, [2]Brigham and Women's Hospital, [3]Harvard Medical School, Boston, MA, United States, [4]University Hospital Zurich, Zurich, Switzerland

Background: Hyponatremia has been shown to be associated with worse outcomes in patients with heart failure. There are however conflicting findings regarding its prognostic value for readmission in patients with heart failure, and in particular whether or not correction of a low sodium level at admission affects the risk of readmission and death.
We assessed whether correction of a low sodium level during a hospital stay impacted on the risk of 30-day unplanned readmission and death in patients with congestive heart failure, as compared to patients who did not have their sodium level corrected before discharge.
Methods: We performed a retrospective study on adult patients admitted with a diagnosis of congestive heart failure between July 2003 and October 2009 at a tertiary-care hospital in Boston, MA. We restricted the analysis to those presenting with hyponatremia at admission. We captured the sodium level at admission and discharge to measure the difference between both. The exposure was categorized in 2 groups: 1) hyponatremia at admission without correction during the hospitalization, defined as a sodium level of less than 135 mmol/l both at admission and discharge; 2) hyponatremia at admission with correction during the hospitalization, defined as a sodium level at admission of less than 135 mmol/l, but 135 mmol/l or more at time of discharge. The primary outcome of interest was a composite of 30-day unplanned readmission or death.
Results: Among the 4,295 eligible patients with hyponatremia at admission, 1,799 (41.9%) did not have their hyponatremia corrected before discharge, over a median length of stay of 6 (IQR 3-9). Overall, 1,269 (29.6%) patients had a 30-day unplanned readmission or died. In a multivariable logistic regression analysis, the absence of hyponatremia correction was associated with a 46% increase in the odds of having a 30-day unplanned readmission or death (odds ratio 1.46 [95%CI 1.27-1.67]; Table)

Table. Multivariable logistic regression for 30-day unplanned readmission or death.

Variable	Odds ratio	95% Confidence Interval
Persistent hyponatremia	1.46	1.27-1.67
Age, per additional year	1.00	1.00-1.01
Female vs. male	1.13	0.98-1.30
Race		
White	ref	
Black	1.31	1.06-1.61
Hispanic	1.32	1.00-1.73
Other	1.24	0.79-1.94
Number of admissions in the last 6 months, per additional admission	1.30	1.24-1.36
Unplanned vs. elective index admission	1.86	1.44-2.39
Length of stay, per additional day	1.01	1.00-1.01
Atrial fibrillation	1.07	0.92-1.24
Ischemic heart disease	0.86	0.74-0.99
Cancer	1.85	1.56-2.20
COPD	1.02	0.85-1.22
Diabetes	1.12	0.96-1.30
Chronic kidney disease	1.03	0.87-1.24

[Table]

The odds ratio for specifically any 30-day unplanned readmission was 1.35 (95%CI 1.17-1.57).

Conclusions: The absence of correction of hyponatremia over the course of hospitalization is frequent and associated with an increase of nearly 50% in the odds of having a 30-day unplanned readmission or death. This may or may not be causal as there is almost certainly confounding by severity of illness, but absence of correction is strongly correlated with a worse outcome.

P322 Low sensitivity of dermal aspirats in patients with cellulitis/erysipelas

Rein Jan Piso[1], Ines Griesshammer[2], Milena Urfer[1], Matthias Wieland[1], Roxana Pop[1], Stefano Bassetti[3]

[1]Medizinische Klinik, Kantonsspital Olten, Olten, [2]Notfall, Inselspital, University Hospital of Bern, Bern, [3]University Hospital Basel, Basel, Switzerland

Background: Cellulitis is normally treated without knowledge of the responsible pathogen. Blood cultures are only positive in about 2-4 %, and superficial swabs show primarily skin colonisation only. Needle aspiration has been proposed with identifying the likely pathogen in up to 29%, but these studies are of older date and the technique is not widely used.

Methods: In February 2013, we introduced this technique as routine diagnostic procedure in patients with erysipelas/cellulitis. Diagnosis was made clinically by the treating physician. The infection disease specialist visited all patients within 48 hours. Needle aspiration was done before introduction of antibiotic treatment from the margin of the inflammation in the first 25 patients. Then we changed the aspiration site to the point of maximal inflammation. With a BDPlastikpak™ Luer 1 ml syringe and a BD Microlane™3 26G ½ " needle 0.3ml sterile NaCl 0.9 % was injected and subsequently directly aspirated. The syringe was brought directly to the microbiological lab. Patients were treated according to local antibiotic guidelines, mainly with amoxicillin/clavulanat. Skin colonisation bacteria were estimated as contamination.

Results: 95 patients were seen during a period of 22 month. 4 patients were excluded, as diagnosis was not confirmed. In 10/91 patients, cellulitis was diagnosed, 81/91 patients presented with erysipelas. In the first 25 patients with needle aspiration from the margin, none was positive. In 8/66 (12 %) patients with needle aspiration from at the site of maximum inflammation, the pathogen was identified by needle aspiration. 4/8 (50%) cultures were positive for S aureus, 2/8 (25%) for streptococci and 2/8 (25%) for other bacteria. In 11/66 (16.6%) patients, skin colonisation flora was detected by aspirate. 11 patients had prior antibiotic treatment. Neither blood culture nor needle aspirates were positive for in these patients. In the subgroup of patients without prior antibiotic treatment and needle aspiration from the site of maximum inflammation,

sensitivity was slightly better 8/56 (14.3%; 95%CI 7.5-25.8%). In 2/66 patients, blood cultures were positive (S. aureus). Needle aspirate was negative in both patients. Antibiotic treatment was not changed in any patient due to results of needle aspiration.
Conclusion: Needle aspiration had a low sensitivity for detecting responsible pathogen in patients with cellulitis/erysipelas. No impact in antibiotic treatment could be observed.

P323 Hepatitis E virus infection: an underdiagnosed disease

Giuseppe Togni, Marylin Aebi, Sacha Giovanetti, Jacqueline Bizet
Laboratoire Central de Suisse Romande, Unilabs SA, Coppet, Switzerland

Introduction: Most of the hepatitis E (HEV) infections occur in the form of major epidemics triggered by fecal contamination of water in endemic areas. Sporadic forms are observed between two epidemics and in non-endemic areas. In industrialized countries, HEV infection is generally suspected in presence of an acute hepatitis, if the anamnesis revealed a recent travel in an area at risk. Nevertheless, cases of HEV were reported without travel, suggesting local infection. Therefore, infection with HEV should be considered in any unexplained acute hepatitis. However, it seems that the infection is still underdiagnosed in industrialized countries.
Recent studies in different European countries have shown great variability in seroprevalence, ranging from 3.2 to 26.7%, that could partially be explained by highly variable performances between currently available commercial tests detecting anti-HEV IgG.
One aim was to assess if HEV infection is underdiagnosed in Western Switzerland. Another aim was to determine the seroprevalence of HEV.
Material: To assess if HEV infection is underdiagnosed, we tested 147 sera that met these following criteria: elevated transaminases (ALAT >100U/l; ASAT >70 U/l) levels; tested negative for hepatitis A, B and C (analyzes requested by the prescriber); analyses for HEV not requested. Each sample was screened (IgG and IgM) with HEV ELISA kit (Diapro).
To determine the seroprevalence 442 sera were selected and screened (IgG) with HEV ELISA kit (Diapro).
Results: Fourteen out of 147 sera (10%) were HEV IgG and IgM positive.
Overall, the prevalence is 25.6% (108 positive/422 samples). However, there is a marked difference between the genders (male: 38.1%, 86/226; female: 11.2%, 22/196), and a significant increase of seroprevalence over the ages (< 31 years: 6.1%, 6/95; 31-50 years: 20.1%, 30/149; 51-70 years: 39.7%, 48/121; >70 years: 42.1%, 24/57).
Conclusion: Ten percent of the selected samples showed the presence of IgG and IgM. This observation suggests that HEV hepatitis infection is underdiagnosed in the Switzerland population. Additional tests are underway to determine which genotypes are involved.
Our results of seroprevalence are similar to those described in other studies. Nevertheless, our positive samples will be tested with a second HEV ELISA kit, in order to compare their performances for use as screening test.

P324 Urine pH determines sex-dependent stone composition in Lausanne kidney stone formers

Isaline Bonnemain[1], Olivier Bonny[2]
[1]Universität Lausanne, Alle, [2]Department of Medicine, Service of Nephrology, CHUV, Lausanne, Switzerland

Introduction: Kidney stone is increasing in prevalence worldwide and represents a significant burden for the health system. If kidney stones are mainly composed of calcium oxalate in both sexes, differences in stone composition between men and women have been described for other stone types. The aim of this work was to search for a relationship between urine pH, a major determinant of stone type and stone composition in females and males stone formers.

Methods: Kidney stone formers seen for a first metabolic work-up in the Service of Nephrology at the CHUV were included between 2008 and 2012. Data collected from each patient included various blood and urinary parameters, as well as age, sex, BMI and blood pressure. Urine pH was measured on two different samples: on 24 hours urine collection by urine test strip and on second fresh morning urine with a pH-meter. Infected urines were excluded.
Results: A total of 383 patients were studied, 276 (72%) men and 107 (28%) women. Stone composition was available for 190 patients. Prevalence of uric acid kidney stones increased in patients with urinary pH< 5.5 compared to those > 6.5 (17% vs. 0% on 24h urine collection and 30% vs. 7% on morning urine). Conversely, calcium-phosphate stones were more prevalent in urine in which pH was > 6.5. Percentage of calcium-oxalate kidney stone was pH-independent. Women presented more calcium-phosphate and struvite stones than men (37% vs 23%). Women had higher urinary pH than men, with respectively mean of 6.23 vs. 6.03.
Conclusion: Composition spectrum of kidney stones depends largely on urine pH, with an enrichment of uric acid stones in patient with urine pH< 5.5 and of calcium-phosphate stones in patients with alkaline urine (pH>6.5). We found that women have higher urine pH and more calcium-phosphate and struvite stones than men. Prevention of kidney stone may need different approaches depending on patient's sex.

P325 Iron metabolism is associated with insulin resistance but not plasma glucose levels in young and healthy adults: a population-based study

Philipp Krisai[1], Stefanie Leib[2], Stefanie Aeschbacher[2], Thomas Kofler[2], Mustafa Assadian[2], John Todd[3], Joel Estis[3], Martin Risch[4], Lorenz Risch[4], David Conen[2]
[1]Innere Medizin, [2]Universitätsspital Basel, Basel, Switzerland, [3]Singulex Inc, Alameda, CA, United States, [4]Labormedizinisches Zentrum Dr. Risch, Schaan, Liechtenstein

Introduction: Blood markers of iron metabolism are strongly related to the occurrence of diabetes mellitus. The aim of our study was to comprehensively investigate the relationships between various body iron markers with a broad range of plasma markers related to glucose metabolism in healthy subjects.
Methods: 2170 healthy adults aged 25 to 41 years were enrolled in a population-based study. Established cardiovascular disease, diabetes or a body mass index >35 kg/m² were exclusion criteria. Data on ferritin and transferrin saturation (TSAT) were available in 2160 participants. Multivariable linear regression models were built to assess the associations of ferritin and TSAT with blood levels of several glucose related biomarkers, including glucagon-like peptide 1 (GLP-1), insulin, homeostatic model assessment-insulin resistance (HOMA-IR), fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). All diabetes markers were log-transformed and all iron markers were standardized for analyses.
Results: Median age of our population was 37 years. In multivariable linear regression analyses, β-coefficients (95% confidence intervals) per 1 standard deviation increase in ferritin were 0.04 (0.02; 0.07, p=0.0008) for GLP-1, 0.06 (0.03; 0.08, p< 0.0001) for insulin, 0.06 (0.04; 0.09, p< 0.0001) for HOMA-IR, 0.004 (-0.00; 0.01, p=0.1) for FPG and -0.004 (-0.01; -0.00, p=0.05) for HbA1c. In similar analyses, β-coefficients (95% confidence intervals) per 1 standard deviation increase in TSAT were -0.07 (-0.09; -0.04, p< 0.0001) for GLP-1, -0.06 (-0.08; -0.04, p< 0.0001) for insulin, -0.07(-0.09; -0.05, p< 0.0001) for HOMA-IR, -0.01 (-0.01; -0.00, p=0.0002) for FPG and -0.01 (-0.01; -0.00, p=0.0007) for HbA1c.
Conclusion: Markers of insulin resistance are strongly related with markers of iron metabolism in healthy subjects. These relationships were much weaker for short term and long term glucose levels. These results provide important insights in the relationships between iron metabolism and diabetes occurrence.

P326 Physical activity and energy expenditure across occupational categories

Stefanie Zogg[1,2], Jonas Mundwiler[1,3], Ulla Maarit Schüpbach-Siira[1], Thomas Dieterle[1], David Miedinger[1,3,4], Jörg Daniel Leuppi[1,3]
[1]Medizinische Universitätsklinik, Kantonsspital Liestal, Liestal, [2]Institut für Bewegungswissenschaften und Sport, Eidgenössische Technische Hochschule (ETH), Zürich, [3]Medizinische Fakultät, Universität Basel, Basel, [4]Abteilung Arbeitsmedizin, SUVA, Luzern, Switzerland

Background: When reintegrating patients into the work process after serious injury or illness, employers and insurance agencies may have to assess the workload a person is capable to perform in order to adequately adjust the job profile. The knowledge of workload and required work capacity may facilitate this process, because a successful resumption of work is highly dependent on these factors. Since physical workload differs considerably between industries, it is mandatory to analyze a wide range of physical work requirements and to assess employees' work capacity across occupational categories. The aim of this study was to investigate energy expenditure (EE), daily steps and physical activity in Swiss employees during work and leisure-time in relation to their aerobic capacity.
Methods: In this cross-sectional study, 300 healthy and full-time employed (80-100%) adults (18-65 yrs) were recruited in the Basel region. Participants were stratified by occupational category according to the International Standard Classification of Occupations (ISCO-88) and were then allocated to one of 3 groups with low (professionals), moderate (white-collar workers) and high occupational activity (blue-collar workers). Average daily steps, activity duration at different intensities, total and active EE were assessed using the SenseWear Mini Armband for 7 consecutive days. Individuals' aerobic capacity (VO_{2max}) was determined by the 20m shuttle run.
Results: Complete data were available from 295 subjects equally distributed across groups (62.4% male, age 33.5±12.5 yrs, BMI 24.4±3.5 kg/m^2). Blue-collar workers showed higher levels of occupational activity in terms of total and active EE, daily steps and activity duration at moderate and high intensity than white-collar workers and professionals (Table 1). In contrast, no significant differences were found for leisure-time activity. Aerobic capacity was increased in group 3 (43.2±0.8 ml/min/kg) compared to 1 (39.4±1.0 ml/min/kg) and 2 (37.5±1.0 ml/min/kg) ($p < 0.001$).

Table 1: Work and non-work related physical activity parameters across occupational groups (n=295)

Variable	Group 1 (n=101) N (%) or Mean ± SD	Group 2 (n=98) N (%) or Mean ± SD	Group 3 (n=96) N (%) or Mean ± SD
Male *	55 (54.5)	38 (38.8)	91 (94.8)
Age [yrs] *	38.0 ± 10.8	34.8 ± 12.4	26.9 ± 11.5
BMI [kg/m^2]	24.2 ± 3.2	24.0 ± 3.7	24.9 ± 3.4
EE work [cal] *	2776.7 ± 459.5	2975.8 ± 547.6	4056.2 ± 614.2
EE recreation [cal] *	2845.4 ± 571.7	2745.8 ± 563.5	3109.9 ± 614.6
AEE work [cal] *	802.1 ± 346.3	1032.1 ± 517.9	2234.6 ± 758.3
AEE recreation [cal]	945.6 ±568.2	888.1 ± 569.5	1056.8 ± 645.1
METs work *	1.6 ± 0.2	1.8 ± 0.3	2.3 ± 0.3
METs recreation	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3
Moderate intensity work [min] *	152.2 ± 63.8	216.7 ± 108.0	394.2 ± 134.1
Moderate intensity recreation [min]	178.4 ± 97.6	181.5 ± 107.5	187.8 ± 109.2
High intensity work [min] *	8.8 ± 8.4	9.7 ± 13.4	27.1 ± 22.6
High intensity recreation [min]	11.8 ± 15.8	9.1 ± 19.5	12.1 ± 15.4
Very high intensity work [min]	2.3 ± 5.4	2.1 ± 4.3	1.5 ± 4.5
Very high intensity recreation [min]	2.2 ± 6.5	2.6 ± 7.5	1.9 ± 9.2
Daily steps work *	9757.2 ± 3041.3	11632.4 ± 3704.5	15174.0 ± 4410.8
Daily steps recreation	9501.6 ± 3903.7	9671.3 ± 4513.8	8448.9 ± 5400.2

AEE, active energy expenditure; BMI, body mass index; EE, energy expenditure; MET, metabolic equivalent; SD, standard deviation. * p<0.001. Occupational group 1 includes professionals, group 2 white-collar workers and group 3 blue-collar workers. Moderate intensity is defined as 3-6 METs, high intensity as 6-9 METs and very high intensity as ≥9 METs.

[Table1]

Conclusion: In a representative sample of a working population we found that blue-collar workers had higher levels of occupational activity and aerobic capacity, while leisure-time activity did not differ between groups. These findings suggest that subjects in low physically demanding jobs do not compensate sufficiently for their inactivity at work, while aerobic capacity appears to be predominantly depending on work activity rather than on leisure-time activity.

P327 High correlation between axillar and ear thermometer in fever detection

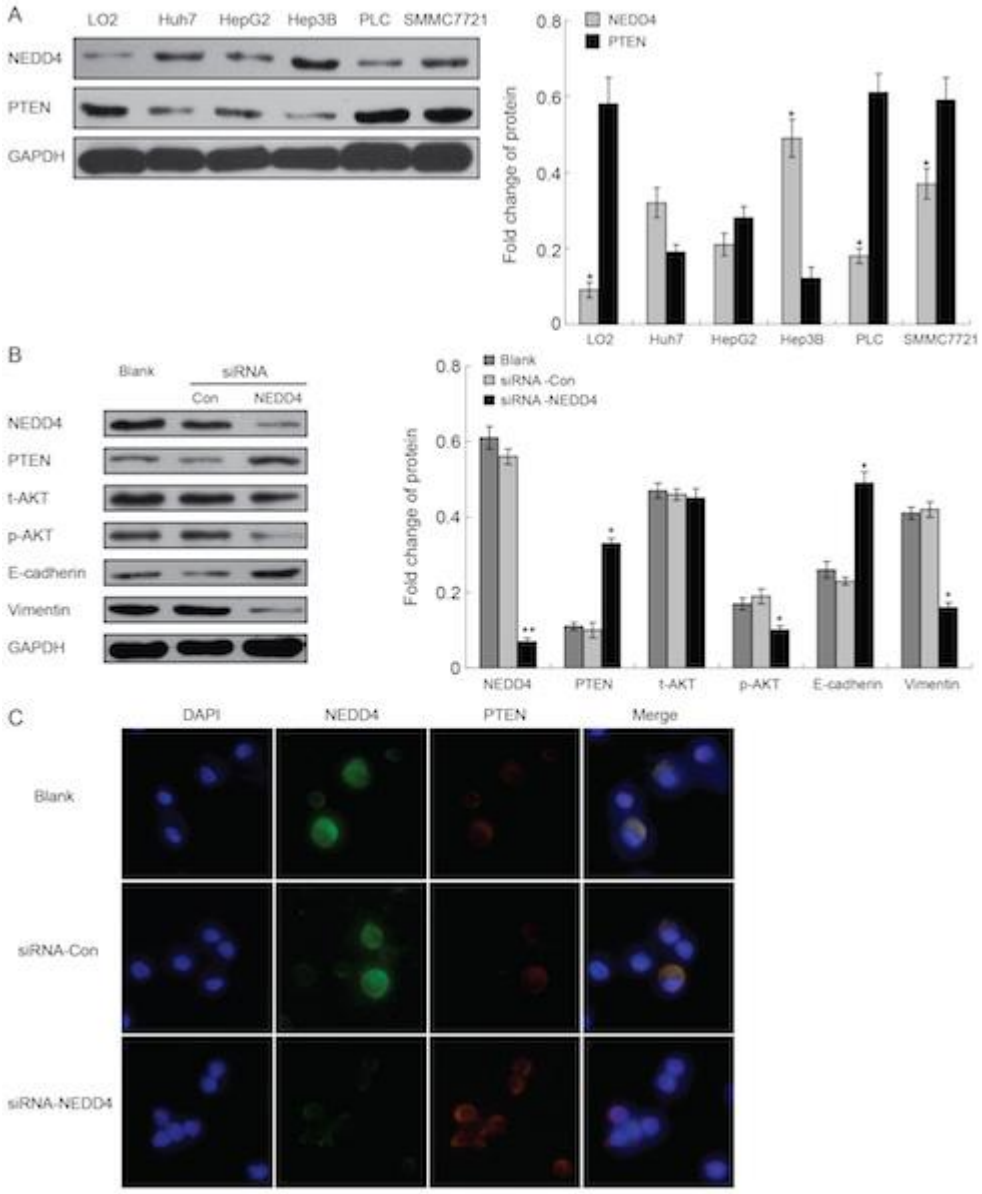
Rein Jan Piso, Claudio Schmutz, Lara Hitz, Lukas Zimmerli
Medizinische Klinik, Kantonsspital Olten, Olten, Switzerland

Background: Ear thermometers are increasingly used in clinical practice. They are convenient and faster than axillar measurement which were used for decades. However, little data on correlation between the two methods exists.
Methods: We with simultaneously measured the body temperature axillary (Terumo Digital Thermometer axillary model C202™) and in the ear (Covidien™) in patients one a regular ward during in July 2013. 465 measurements were done on total 62 patients, mean 7.5 ±5.4 per patient. Correlation (ANOVA regression analysis) and mean differences (ttest for paired data) between the two methods were calculated.
Results: A high correlation between axillary and ear measurement was found r^2=0.59, p< 0.001. Ear temperature was mean 0.04 ^{0}C higher than axillary measurement. In 220/465 measurements (46.8% CI95 42-51%), ear temperature was slightly higher, in 190/465 (41% CI 95 36.5-45.3%), axillary temperature was slightly higher, and in the 55/465 (12% CI95 9.2-15.1) measurements, no difference was found. In 76/465 measurements (16.3 % CI 95 13.2-20%), the difference was more than 0.5 ^{0}C, and in 6/465 (1.2% CI 9500.6-2.8%) difference was more than 1 ^{0}C. Also in the measurements with high differences, the percentage of higher value was equally matched between the two methods.
Conclusion: A high correlation between ear and axillary temperature measurement was found. No trend towards higher or lower measurement in one of the two methods could be found.

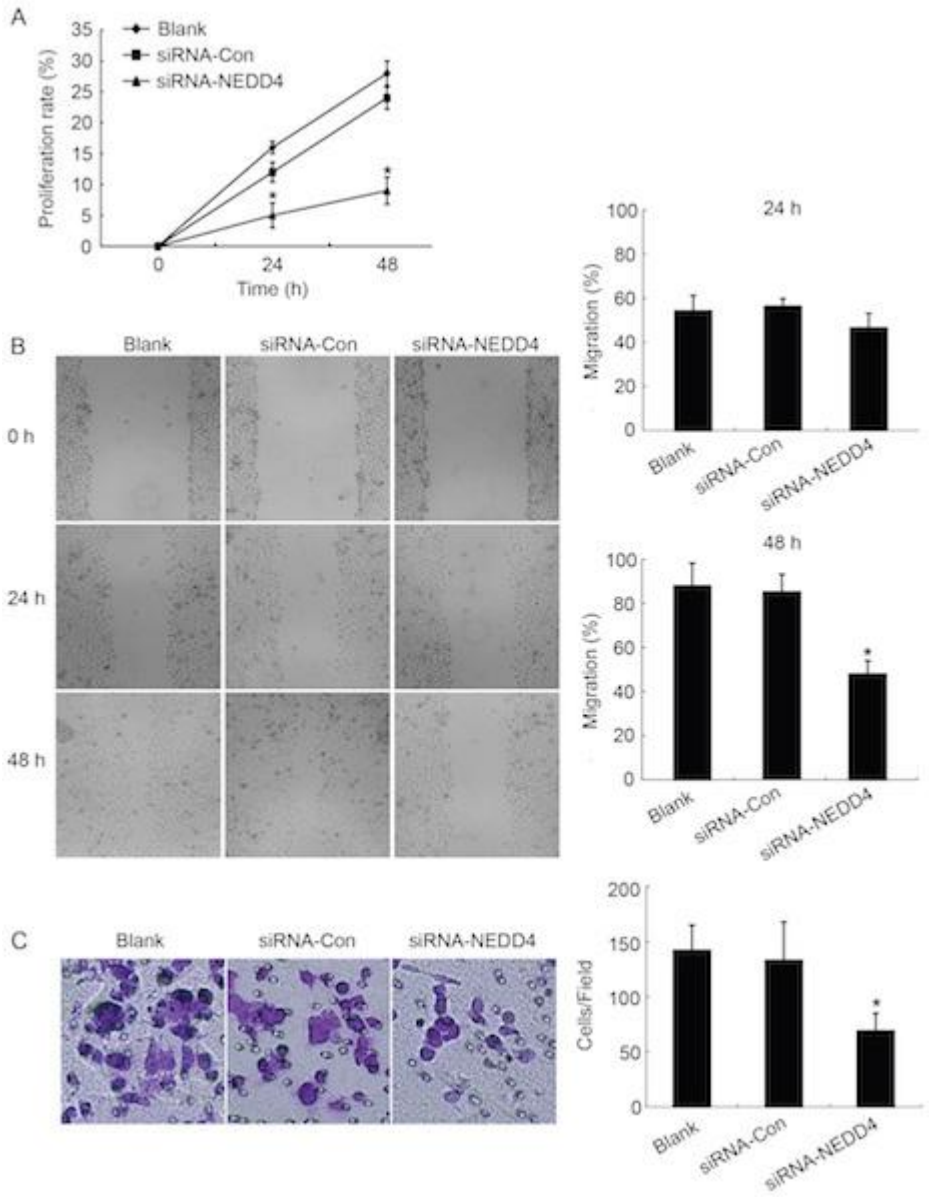
P328 NEDD4 promotes cell growth and migration through PTEN/PI3K/AKT signaling pathway in hepatocellular carcinoma

Ewelina Biskup[1,2], Xiao Yu Yang[3], Zhi Jun Huang[4], Jun Jun Zhi[5]
[1]SICU, University Hospital of Tongji Yangpu, Shanghai, China, [2]Onkologie, Innere Medizin, Universitätsspital Basel, Basel, Switzerland, [3]Eastern Hepatobilary Surgery Hospital, Second Military Hospital, Shanghai, [4]Department of General Surgery, First People's Hospital of Yan Chen, Jiangsu, [5]Department of Radioactive Intervention, Eastern Hepatobiliary Surgery Hospital, Second Military Hospital, Shanghai, China

Background: Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and over the recent years, its incidence has been showing an increasing trend. Despite intensive research of early diagnostics and tumor therapies, including hepatic resection liver transplantation and minimally invasive therapies, the overall prognosis of HCC patients remains poor due to its high rate of metastasis and recurrence.
Neural precursor cell-expressed developmentally down-regulated protein 4 (NEDD4) is a novel E3 ubiquitin-protein ligase. It widely expresses in mammalian tissues and plays a crucial role in tumorigenesis in several cancer types by regulating cell proliferation, migration, and differentiation. The study aimed to investigate the role of NEDD4 as an oncoprotein by targeting the tumor suppressor PTEN (phosphatase and tensin homolog) in hepatocellular carcinoma cells.
Methods: We investigated the expression of NEDD4 and PTEN in normal hepatic and hepatocellular carcinoma cell lines. We aimed to evaluate whether depletion of NEDD4 was influencing HCC cell proliferation and migration via siRNA. Additionally, we observed possible impact on the PTEN/PI3K/AKT signaling pathway.
Results: The protein expression of NEDD4 in HCC cells is increased compared to normal liver cells. Analogically, PTEN is decreased in HCC cells. NEDD4 interacts...MTT assay wound healing experiment and transwell assays confirmed that depletion of NEDD4 decreases the proliferation and migration ability of HCC cells. Western blot and immunofluorescence results revealed that NEDD4 could affect PTEN/PI3K/AKT signaling pathway in HCC cells. Depletion of NE...
Conclusions: Our results indicate that NEDD4 plays a critical role in activating PTENPI3K/AKT signaling pathway, which promotes HCC cells proliferation and metastasis . Therefore, NEDD4 may be a potential target in the treatment of hepatocellular carcinoma.



[NEDD4 interacts with PTEN/PI3K/AKT signaling pathw]



[Depletion of NEDD4 inhibited proliferation, migrat]

Postertour 1:

Allgemeine Innere Medizin 1

Médecine interne générale 1

P329 Estimation of malnutrition prevalence in Internal Medicine using administrative data: not as simple as it seems

Saman Khalatbari Soltani, Peter Vollenweider, Gérard Waeber, Pedro Marques-Vidal
Département de Médecine, Médecine Interne, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Objective: To assess the prevalence of malnutrition in an internal medicine ward according to different definitions, using hospital administrative data.

Methods: Discharge data from the Department of Internal Medicine of the Lausanne University Hospital from 2002 to 2013 (N=43,166 patients aged ≥18 years). Prevalence of malnutrition was assessed using four definitions: 1) any International Classification of Diseases (ICD-10 code) E40 to E46; 2) ICD-10 code R63 or R64; 3) prealbumin levels < 15 mg/dL in any measurement and 4) any of the previous ones. Agreement between definitions was also assessed.
Results: Overall prevalence (95% CI) of malnutrition was 2.7% (2.5-2.9) for definition 1; 1.7% (1.6-1.9) for definition 2; 3.5% (3.3-3.7) for definition 3 and 7.6% (7.3-7.8) for definition 4. No differences in prevalence were found between genders or age groups using definitions 1 and 2, while higher prevalences were found in men and in younger patients using definitions 3 and 4 (table). Of the 1151 patients with prealbumin levels < 15 mg/dL, only 81 (7.0%) were reported as malnourished in discharge data (definition 1) and only 24 (2.1%) were malnourished according to definition 2.
Conclusion: Prevalence and determinants of hospital malnutrition vary significantly according to the definition applied. Professionals filling the discharge letter seem to disregard malnutrition status objectively assessed using prealbumin levels.

	Code E40 to E46	Code R63 or R64	Prealbumin<15 mg/dL	All
Gender (%)	p=0.27	p=0.10	p<0.001	p=0.04
Women	2.79	1.84	2.98	7.24
Men	2.59	1.61	4.01	7.86
Age group (%)	p=0.13	p=0.22	p<0.001	p<0.001
30-59 years	2.90	1.82	4.75	8.91
60-69 years	3.02	1.71	4.93	9.20
70-79 years	2.63	1.43	3.99	7.75
80-89 years	2.40	1.86	1.85	5.9
90+ years	2.51	1.85	1.26	5.47

[Malnutrition prevalence (%) according to gender an]

P330 Emergency medical services interventions for nursing home residents

Pierre-Nicolas Carron[1], Fabrice Dami[1], Bertrand Yersin[1], Valérie Toppet[2], Bernard Burnand[2], Valérie Pittet[2]
[1]Emergency Department, Centre Hospitalier Universitaire Vaudois, CHUV, [2]Institute of Social & Preventive Medicine, Lausanne, Switzerland

Introduction: In the ageing European population, the proportion of prehospital emergency medical services (EMS) for elderly patients is increasing, but little is known about the recent trend of EMS interventions in nursing homes (NH). We aimed to describe the evolution of the incidence of requests to prehospital EMS interventions in nursing homes in a Swiss canton between 2003 and 2012.
Methods: We used the routinely and prospectively collected data for each EMS intervention in the Canton of Vaud (750'000 inhabitants). Linear time trends of incidence of requests to EMS in NH were calculated and stratified by age categories.
Results: Between 2003 and 2012, the overall population of the Canton of Vaud increased from 635'850 to 729'971 inhabitants (+ 14.8 %), and the nursing home population increased from 5862 to 6553 residents (+ 11.8 %). The total number of ambulance interventions in NH increased by 40% (1115 to 1563) between 2003 and 2010. A linear increase of the annual incidence of requests to EMS per 1000 NH residents was observed in all age categories, especially and significantly for people aged 80-89 (11.2, 95%CI: 8.5-13.8) and 65-79 (9.0, 95%CI: 2.4-15.5). For EMS interventions that required an emergency physician (EP), the total number of interventions in NH increased from 2% (N=111) to 7% (N=311) of all interventions, especially for people over 80.

Conclusions: Our results confirm an important increase in the incidence of EMS interventions in NH during the last decade. This evolution represents a main opportunity to redesign anew the roles and missions of EMS in the context of an ageing society. Due to population ageing, changes in societal values and expectations regarding life-threatening and acute situations, which occur in the context of limited resources, overcrowding of ED and the relative unavailability of GPs, we definitely need to revise EMS paradigms.

We should move from the classical concept of the "survival chain", conceptualized to provide a transport to the hospital, to a patient-centered approach, using EMS resources to adequately manage and triage patients, and to prevent unnecessary ED admissions.

P331 Association of occupational and leisure time physical activity with aerobic capacity in a working population

Jonas Mundwiler[1,2], Stefanie Zogg[1,3], Ulla Schüpbach[1], Thomas Dieterle[1,2], David Miedinger[4], Jörg Daniel Leuppi[1,2]
[1]University Department of Internal Medicine, Cantonal Hospital Baselland, Liestal, [2]Medical Faculty, University of Basel, Basel, [3]Institute of Human Movement Sciences and Sport, ETH Zurich, Zurich, [4]Department of Occupational Medicine, Swiss National Accident Insurance Institution (Suva), Lucerne, Switzerland

Background: Although several studies have been made to investigate the relationship between physical activity and aerobic capacity (VO_2max) in employees, there are few objective data available so far. Thus, the potential positive effects of work and leisure-time physical activity on aerobic capacity still remain unclear. Therefore, the objective of this study was to investigate the association between work and non-work related physical activity and aerobic capacity in a Swiss working population.
Methods: In this cross-sectional study, a total of 300 healthy and at minimum 80% employed workers of the Basel region were investigated. Demographic data, height, weight and waist circumference were recorded in all subjects. Energy expenditure and physical activity were measured with the SenseWear Mini Armband for seven consecutive days (23 hours/day). Aerobic capacity was evaluated using the multistage 20 meter shuttle run test.
Results: Complete data were available for 295 subjects (62.4% male, age 33.5 ±12.5 yrs, BMI 24.4±3.5 kg/m^2). The forced-entry multiple linear regression analysis with aerobic capacity as dependent variable showed significant associations of aerobic capacity with occupational physical activity of moderate to vigorous intensity (Table 1). R-Quadrat of the analysis was 0.63. Furthermore, age, gender and body mass index (BMI) contributed significantly to the model. In contrast, leisure time physical activity (LTPA) and energy expenditure were not found to be independent predictors of aerobic capacity.
Conclusion: The present results suggest that occupational physical activity significantly affects aerobic capacity in a Swiss working population. Aerobic capacity was found to depend highly on occupational physical activity, particularly when the intensity of physical activity is in the moderate-to-vigorous range. In contrast, leisure-time activity does not appear to be predictive for aerobic capacity in a working population.

Table 1. Forced-entry multiple linear regression analysis with VO_{2max} as dependent variable (n=295)

Variable	Regression coefficient B	SE B	β	p value
Constant	87.28	4.56		0.000
Gender	-12.34	1.09	0.65	**0.000**
Age	-0.21	0.03	-0.28	**0.000**
BMI	-1.14	0.19	-0.42	**0.000**
EE work	0.00	0.00	0.12	0.466
EE recreation	0.00	0.00	0.03	0.819
Moderate PA work	-0.03	0.01	0.42	**0.001**
Moderate PA recreation	0.01	0.01	0.09	0.388
High PA work	0.10	0.03	0.19	**0.001**
High PA recreation	-0.16	0.03	0.03	0.599
Very high PA work	0.24	0.09	0.13	**0.005**
Very high PA recreation	0.19	0.06	0.16	**0.002**
Steps work	0.00	0.00	0.12	**0.039**
Steps recreation	0.00	0.00	0.09	0.125

BMI, body mass index; β, standardized beta-coefficient; EE, energy expenditure; Moderate / High / Very high PA, physical activity duration at moderate (3-6 METs) / high (6-9 METs) / very high (≥9 METs) intensity; PA, physical activity; SE, standard error. VO_{2max}, maximal oxygen consumption during multistage 20 m shuttle run test. Significant *p* values are highlighted in bold.

[Table_1]

P332 Five year trends in dyslipidaemia prevalence and management in Switzerland: the CoLaus study

Panagiotis Antiochos, Pedro Marques-Vidal, Martin Preisig, Gérard Waeber, Peter Vollenweider
CHUV, Lausanne, Switzerland

Introduction: Little is known regarding trends over time of dyslipidaemia and its treatment in Switzerland.
Methods: Data from the prospective population-based Colaus study at baseline (2003-2006) and follow-up (2009-2012). Cardiovascular (CV) risk was stratified using PROCAM score. Dyslipidaemia and low-density lipoprotein (LDL-C) target levels were defined according to 2011 ESC/EAS guidelines.
Results: Of the initial 6733 participants in baseline, 4929 (2639 women, mean age 57.8±10.5 years) were included for analysis. At follow-up, 46.5% of the sample presented with dyslipidaemia, of which 39.8% were treated and 59.4% of those treated were controlled. Among subjects with known cardiovascular disease, 54% were treated, of which 16.5% had a LDL-C≤1.8mmol/l. Lipid lowering medication (LLM) treatment was positively associated with older age (odds ratio (OR)=1.28, 95% confidence intervals (95% CI): 1.22-1.34),

diabetes (OR=1.80, 95% CI: 1.42-2.28), higher body mass index (BMI) (OR=1.31, 95% CI: 1.18-1.45) and negatively associated with higher educational level (OR=0.73, 95% CI: 0.61-0.88). Male sex (OR=0.61, 95% CI: 0.42-0.89), older age (OR=0.89, 95% CI: 0.80-0.98) and higher BMI (OR=0.80, 95% CI: 0.67-0.97) were associated with poorer control of LDL-C levels, while diabetes (OR=1.73, 95% CI: 1.14-2.61) was related to better control.
Compared to baseline (2003-2006), after a mean duration of 5.6 years, the number of LLM prescriptions increased by 85% (n=530 vs n=982). Despite that, the proportion of untreated dyslipidaemia in the sample increased due to n=1164 (24%) subjects moving to a higher cardiovascular risk category as a result of ageing and an increase in absolute LDL-C values (3.32±0.9mmol/l vs 3.45±0.93mmol/l, p< 0.001) in the sample. Older age (OR=1.13, 95% CI: 1.05-1.22) and higher BMI (OR=1.23, 95% CI: 1.05 - 1.45) were positively related to LLM prescription. During the follow-up period, a hundred subjects discontinued their LLM, with male sex (OR=0.50, 95% CI: 0.29-0.85), older age (OR=0.67, 95% CI: 0.58-0.77) and higher BMI (OR=0.71, 95% CI: 0.53-0.94) being negatively associated with LLM interruption.
Conclusion: Over a 5.6-year follow-up, dyslipidaemia prevalence increased in the community along with LDL-C levels. Although use of LLM significantly increased, there is still great potential for detection, treatment and control of dyslipidaemia, both in primary and secondary prevention.

P333 Independent association of earlobe crease with cardiovascular risk factors and diseases: the CoLaus study

Marta Aligisakis[1], Peter Vollenweider[1], Pedro Marques-Vidal[1], Idris Guessous[2]
[1]Médecine Interne, CHUV, Lausanne, [2]HUG, Genève, Switzerland

Background: Earlobe crease (ELC) has been associated with cardiovascular disease (CVD) and risk factors (CVRF), especially higher BMI and hypertension, and could be a marker predisposing to CVD. However, the associations were usually limited to a small number of CVRF and the mechanisms involved are poorly understood.
Methods: Data from the first follow-up of population-based CoLaus study (n=4635, 46.7% men) conducted between 2009 and 2012 in Lausanne, Switzerland.
Results: Of the 4635 participants, 806 (17.4%) had an ELC, of which 373 (46.3%) unilateral. Presence of ELC was associated with age, male gender, higher body mass index (BMI), abdominal obesity, hypertension, higher glucose and insulin levels, diabetes, insulin resistance, dyslipidaemia (especially lower HDL cholesterol and higher triglycerides levels), metabolic syndrome (MS) and history of CVD. In multivariate analyses adjusting for age and gender, ELC remained significantly associated with abdominal obesity [odds ratio and (95% confidence interval) 1.20 (1.02; 1.42)]; hypertension [1.41 (1.18; 1.67)]; diabetes [1.43 (1.15; 1.79)]; high HOMA-IR [1.53 (1.18; 1.99)]; lower HDL cholesterol and higher triglycerides levels (p-value < 0.05), MS [1.28 (1.08; 1.51)] and history of CVD [1.55 (1.21; 1.98)]. However, when BMI was added to the model, only the associations between ELC and hypertension [1.30 (1.08; 1.56)], glucose level (p-value < 0.05) and history of CVD [1.55 (1.21; 1.98)] remained significant.
Conclusion: In this community-based sample we observed a significant association between ELC and some classical cardiovascular risk factors (particularly higher BMI and hypertension) but also with a positive history of CVD.

P334 Determinants of the health-related quality of life of patients surviving acute coronary syndromes: data from the Swiss ELIPS study

Baris Gencer[1], Nicolas Rodondi[2], Reto Auer[3], David Nanchen[4], Lorenz Räber[5], Roland Klingenberg[6], Christian M. Matter[6], Stephen Windecker[5], Peter Jüni[7], Thomas Felix Lüscher[6], François Mach[8], Thomas Perneger[9], Girardin François[9]
[1]Division of Cardiology, Geneva University Hospitals, Genève, [2]Department of General Internal Medicine, Bern University Hospital, Berne, [3]Department of Ambulatory and Community Medicine, Lausanne University, Genève, [4]Department of Ambulatory and Community Medicine, Lausanne University, Lausanne, [5]Department of Cardiology, Bern

University Hospital, Bern, [6]Department of Cardiology, University Heart Center, Zürich, [7]Institute of Social and Preventive Medicine, Bern, [8]Division of Cardiology, Geneva University Hospitals, Geneva, [9]Division of Clinical Epidemiology, Medical Directorate, Geneva University Hospitals, Genève, Switzerland

Background: Health-related quality of life (HRQoL) reported by the patients became a standard for decision making of health intervention. Patients surviving after acute coronary syndromes (ACS) present a wide spectrum of clinical conditions that might affect the applicability of reference values of HRQoL.
Methods: We measured systematically HRQoL estimates by EuroQol five-dimensional (EQ-5D) health utility and visual analog scale (VAS) at 12-month follow-up of 1866 patients who were hospitalized for ACS in Switzerland from 2009 to 2012 (ELIPS Study, NCT 01075867). A linear multivariate model was built to assess associated clinical factors with HRQoL estimates. We compared the expected mean (±SD) values of the EQ-5D utility index and VAS among ACS survivors by means of a validated formula based on age and sex derived from the Swiss general population.
Results: In ACS patients, the most affected domains of EQ-5D were pain (46.6%) and anxiety (34.0%), while 39.6% of subjects had the highest utility. Associated clinical factors with lower EQ-5D utility index estimates were women, lower education, diabetes, hypertension, obesity, heart failure signs during ACS hospitalization, persisting elevated heart rate and non-attendance to cardiac rehabilitation ($P < 0.05$). Observed values of the EQ-5D index compared to values in the general population were similar in men (0.82±0.16 vs. 0.82±0.03, $P = 0.71$) and in women (0.77±0.17 vs. 0.78±0.03, $P = 0.21$), while the VAS was significantly lower in men (77.1±17.3 vs. 79.4±4.1, $P < 0.001$) and in women (72.1±18.3 vs. 77.4±4.7, $P < 0.001$).
Conclusions: HRQoL of patients surviving after ACS did not significantly differ from the reference values of the Swiss general population for the EQ-5D utility index estimates, but were significantly lower for the VAS. These results are important for future medico-economic studies and the assessment of health technologies by policy makers for the Swiss ACS population.

P335 Pyroglutamic acidemia: an unusual cause of high anion gap acidosis

David Gachoud[1], Pierre Métrailler[2], Alejandra Martiz Aguilar[2], Peter Vollenweider[2]
[1]Service de Médecine Interne - CHUV et Unité Pédagogique, Faculté de Biologie et de Médecine (FBM), UNIL, [2]Service de Médecine Interne, CHUV, Lausanne, Switzerland

Case description: A 59-year-old man was admitted to our hospital because of acute abdominal and dorsal pain. His comorbidites included chronic renal failure (stage 3), hypertension and type II diabetes. After being admitted, he developped fever (38.0°C), and blood cultures were positive for methicilline-sensitive *S. aureus*. Diagnostic workout consisted in echocardiography, thoraco-abdominal CT and dorso-lumbar MRI. The latter showed an important epiduritis (D3-D9), with D5-D7 spondylodiscitis. Flucloxacilline was started. At the admission, an acute kidney injury superimposed on the chronic kidney disease (creatinine 266 µmol/l). Arterial blood gases showed a metabolic acidosis with insufficient respiratory compensation (pH 7.28; PaCO2 38.8 mmHg; bicarbonates 16.8 mmol/l; BE - 9.3 mmol/l). This was attributed to the acute kidney injury, after usual causes had been excluded (no lactate, no cetones, no evidence for methanol, ethylene glycol, paraldehyde, salicylates). Despite improvement of renal function (creatinine 175 µmol/l), metabolic acidosis worsened (pH 7.24; bicarbonates 12.7 mmol/l; BE - 13.3 mmol/l). Anion gap was high (23.9 mmol/l). Patient condition was characterized by a progressive alteration of consciousness and myoclonia. Head CT and EEG did not yield a diagnosis. On day 26, the patient was comatous and needed intubation for airway protection.
Finally, we obtained the results of urinary pyroglutamic acid, which was elevated at 2232 mmol/mol creatinine (normal value < 43). Our diagnosis was pyroglutamic acidemia. We started IV N-acetyl-cysteine. Three days later, metabolic acidosis was corrected, and the patient could be extubated with improved level of counsciousness.
Pyroglutamic acidemia: Pyroglutamic acidemia is an unusual cause of high anion gap acidosis. Pyroglutamic acid (or 5-oxoproline) is an intermediary product in the γ-glutamyl cycle. It accumulates when glutathione stores are depleted. In case of glutathione deficiency, the activity of γ-glutamylcysteine

synthetase is increased. This results in increased amount of γ-glutamyl cysteine, which is thereafter converted in pyroglutamic acid. Glutathione deficiency occurs for various reasons: therapy with paracetamol, malnutrition and probably sepsis. In our case, paracetamol and an acute infection were present. Finally, an additional factor played a role in our patient. Indeed, flucloxacilline inhibits 5-oxoprolinase, which normally breakdowns pyroglutamic acid.

P336 Lung cancer screening in workers with a history of asbestos exposure

Julia Christin Sanchez Perez[1,2], Claudia Pletscher[2], Susanna Stöhr[2], Jörg Daniel Leuppi[1], Michael Koller[2], David Miedinger[2]
[1]Innere Medizin, Kantonspital Liestal, Liestal, [2]Arbeitsmedizin, SUVA, Luzern, Switzerland

Introduction: The National Lung Cancer Screening Trial (NLST) showed, that lung cancer specific mortality can be reduced among people with elevated risk for primary lung cancer by using annual low dose computer tomography. Since 2011 workers with former or ongoing asbestos exposure undergo statutory health surveillance offered by Suva. We conducted an audit of this program to obtain information about the quality, the practicability, the adherence to inclusion criteria and the screening protocol as well as the pulmonary findings obtained.
Methods: We analyzed data from the first 175 consecutive workers. Included were current or former asbestos exposed workers at the age of 55 to 75 years, with an asbestos exposure (>0.1 fiber-years) and cigarette consumption of more than 30 pack years (Group A) or workers with an estimated asbestos exposure of>=25 fiber-years with or without cigarette consumption (Group B). Workers underwent three annual screening rounds with low-dose computer tomography (LDCT). Non-calcified nodules of >= 4, pleural plaques or asbestosis were considered as positive screening result. False positive rate was defined as the rate of positive exams without a cancer diagnosis within one year.
Results: The mean age was 68 years (57 to 75 years). 172 workers (98%) were male. Seventy-eight workers (45%) were classified in Group A and 97 individuals (55%) were classified in Group B. One hundred forty-six workers underwent all screening rounds (83%). Positive findings were found in 95 workers (54%) (31% Pleural plaques [n = 54], 21% lung nodules >= 4mm [n = 37] workers and 21% asbestosis [= 19]. A total of 29 workers (17%) had lung nodules >=4 mm without a cancer diagnosis within one year (false positive rate). Further investigations were required in 24 workers (14%). The prevalence of primary lung cancer was 2% [n = 3]. All cancers were diagnosed in context of the screening program and all were in potentially curable stages (Stage IA [n = 2], Stage IIA [n = 1]). Four workers died from causes other than lung cancer (mesothelioma [n = 1], unclear [n = 3]).
Conclusions: In workers with occupational asbestos exposure and high risk for lung cancer, the rate of positive CT findings was higher than in the NLST, however the proportion of false-positive findings was lower meaning fewer unnecessary invasive investigations were performed. LDCT can detect cancers in potentially curable stages in a population of workers with former or ongoing asbestos exposure.

Postertour 1:

Allgemeine Innere Medizin 2

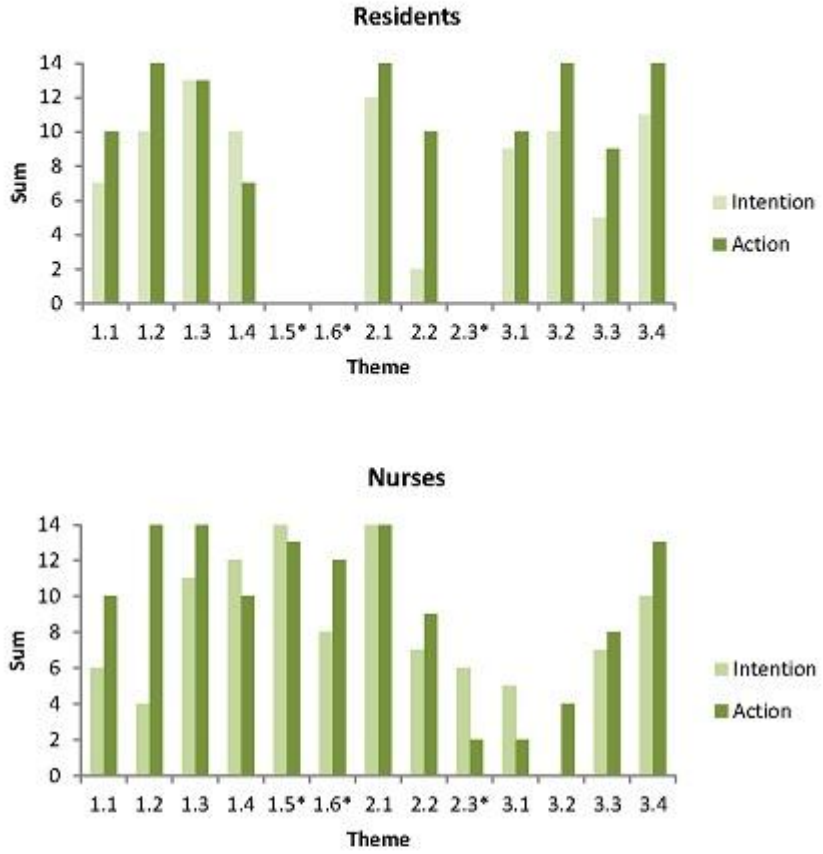
Médecine interne générale 2

P337 Do residents and nurses translate their role perceptions into action? A study in the context of an internal medicine war

Virginie Muller-Juge[1], Naïke Bochatay[1], Fabienne Scherer[2], Guillemette Cottin[3], Stéphane Cullati[4], Katherine S. Blondon[5], Patricia Hudelson[6], Fabienne Maître[5], Nu V. Vu[1], Georges L. Savoldelli[7], Mathieu R. Nendaz[5]
[1]Unité de Développement et de Recherche en Education Médicale, Université de Genève/Faculté de Médecine, [2]Hôpitaux Universitaires de Genève, [3]Université de Genève/Faculté de Médecine, [4]Service Qualité des Soins, [5]Service de Médecine Interne Générale, [6]Département de Médecine Communautaire et de Premier Recours et des Urgences, [7]Service d'Anesthésiologie, Hôpitaux Universitaires de Genève, Genève, Switzerland

Introduction: Studies on interprofessional collaboration mostly focus on role perceptions or on actions, but not on the association between perceptions and actual actions. The aim of our study was to analyze the association between residents' and nurses' own role perceptions and their actual translation into action. We aimed at identifying themes for which participants' actions either matched or did not match their perceptions.
Methodology: A volunteer sample of 14 residents and 14 nurses was recruited from our General Internal Medicine Division. First, participants were individually interviewed about their own role perceptions and their intended roles in two paper-based cases. Second, each nurse was randomly paired with a resident to manage two cases in a simulated Internal Medicine ward, using a high-fidelity manikin. For the present study, the datasets of both steps were tabulated to evaluate the level of concordance between participants' perceptions and actual actions, a process which was verified by a thorough qualitative analysis of part of the data. We used descriptive and kappa statistics to assess general features of the data and explored the features' details qualitatively.
Results: Preliminary results suggest that overall, there is a significant but weak correlation between themes mentioned as important in role perception and their translation into action, either for residents (kappa 0.20, $p=0.007$) or for nurses (kappa 0.27, $p< 0.001$). Overall, more themes were present in action than during the interviews, both for residents ($p< 0.011$) and nurses ($p< 0.001$). This was true for themes such as having "common objectives", "verification" of the other's work, or "help, availability". Some themes were equally mentioned and performed by all participants (e.g. "technical information sharing"), but other ones appeared more frequently in interviews than in actions (e.g. "dependence" on the other professional, "feedback" to the other professional, "team building"), with some variations depending on the profession.

Occurrence of different themes in participants' intentions and actions, by profession



Themes:

1. Autonomy, reflection and leadership	
1.1	Shared decision
1.2	Common objectives
1.3	Decision, reasoning, anticipation, proactivity
1.4	Dependence
1.5*	Implication, understanding
1.6*	Opinion giving, suggestion
2. Technical communication	
2.1	Technical information sharing and communication
2.2	Verification
2.3*	Organization, planning, prioritization
3. Manifestations regarding team building	
3.1	Debriefing, feedback, valorisation, moral support
3.2	Training
3.3	Help, availability
3.4	Team building
*	Indicates themes that are specific to nurses and did not appear in residents' perceptions and actions

[Occurence of different themes]

Conclusion: There are some discordances between residents' and nurses' role perceptions and their translation into action; discordant themes may represent topics for better role clarification and training, in order to increase their translation into action.

P338 Quality of care of patients with diabetes: impact of foregoing care because of costs

Isabelle Peytremann-Bridevaux, Emilie Zuercher, Bernard Burnand
CHUV, Institut universitaire de médecine sociale et préventive, Lausanne, Switzerland

Introduction: In general population surveys, about 15% of participants report foregoing care because of costs. It remains unclear whether patients with chronic diseases forego care because of costs, and if yes, whether it has any impact on the quality of their care. We aimed at examining these two issues in Swiss diabetic patients.
Methods: Self-reported baseline and 2-year follow-up data collected from non-institutionalized adult patients with diabetes residing in the canton of Vaud (Co-DiabVD cohort). The main exposure variable was foregoing care because of costs, and dependent variables were quality of care indicators: annual eye, urine, foot and lipids checks, influenza immunization, past year hospitalization, generic and disease-specific quality-of-life, HbA1C, blood pressure, self-efficacy, overall satisfaction. Linear and logistic regressions were performed adjusting for potential confounders (age, gender, marital status, socio-economic status) and baseline values of quality of care indicators.
Results: Patients foregoing care because of costs were younger (61.0 vs 64.9 years), mostly women (50.6% vs 37.5%), reporting a household income below median (60.8% vs 44.3%) and in poorer subjective health (38.5% vs 18.5%) compared to those not foregoing care. Both groups reported similar outpatient healthcare utilization. At 2 years, adjusted results showed that patients foregoing care did not report worse processes or outcomes across a range of quality of care indicators.
Conclusions: Patients with diabetes reporting foregoing care because of costs presented worse health status, more difficulties managing their disease and less care satisfaction. However, foregoing care did not have any impact on their two-year self-reported quality of care.

P339 Knowledge translation in medicine: sources of information and barriers to implementation

Bernard Burnand[1], Emilie Bovet[1], Theresa Bengough[1], Michael Amiguet[1], Alpha Barry[1], Vincent Pidoux[1], Francesco Panese[2], Michèle Grossen[2]
[1]Lausanne University Hospital, [2]Faculté des sciences sociales et politiques, Université de Lausanne, Lausanne, Switzerland

Introduction: Physicians are exposed to constantly increasing new information. Barriers to knowledge translation generate delays to adopting new effective interventions, persistence of obsolete treatments, overuse of ineffective interventions and underuse of effective care, contributing thus to a “know-do-gap”. Our objective was to examine current knowledge translation practices in medicine in Switzerland. **Methods:** Using mixed methods, we conducted first a qualitative study (semi structured open ended interviews and focus groups) targeting family physicians, psychiatrists, cardiologists, endocrinologists, and orthopaedic surgeons (autumn 2013) in Switzerland. A computer assisted web interview (CAWI) of a large sample of these groups of physicians was conducted (Summer 2014), using a questionnaire based on the literature and the analyses of interviews and focus groups, targeting sources of and barriers to information, and adherence to evidence-based medicine (EBM) principles. We computed a score of adherence to EBM based on 5 items and used uni- and multivariate analyses.
Results: 29 family physicians (21 men) participated to the qualitative study and 985 to CAWI (15% participation, similar among the three Swiss language regions and physicians' specialty; 587 family physicians). Analyses of the qualitative study indicated that colleagues and specialists were a main source of information, as well as medical journals (paper and internet), trainees and patients. Main barriers included patients' beliefs, knowledge and communication gaps between family and specialist physicians, lack of time and of appropriate guidelines for daily practice. CAWI indicated that the main three sources of information of family physicians included congresses (41%), practice guidelines (38%), colleagues (37%), specialists (33%), systematic reviews (28%), knowledge syntheses (24%) and quality circles (21%). Adherence to EBM was very high in 25%, high in 51% and (very) low in 24% of physicians. Adherence to EBM decreased slowly with age, was lower In the French language region, highest in cardiologists and lowest in psychiatrists and orthopaedic surgeons.

Discussion: We observed that physicians working in Switzerland use various sources of information to update their knowledge, but that no one dominates. Evidence-based sources are often used and three quarters of physicians adhere to its principles. The optimal source, type and format of information for busy physicians are uncertain.

P340 Does age matter in the out-of-hospital clinical decisions in emergency situations for the SMUR (Service mobile d'Urgences et de Réanimation) in Switzerland (canton of Vaud) in the missions between 2005 and 2013

Vânia Tavares[1], Bernard Burnand[1], Pierre Nicolas Carron[2]
[1]Institute of Social and Preventive Medicine, Lausanne University Hospital, [2]Urgences, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Background: By 2050, more than 10% of the population will be over 80 years old, compared to 3.7 today. The average age of patients supported by the out-of-hospital emergency services is already increasing in parallel. This evolution raises questions about the optimal management of these patients.
Among the papers about age in the out-of-hospital setting, many authors have studied the predictors of successful resuscitation and survival after an out-of-hospital cardiac arrest. It was found that age is not an independent predictor of poor prognosis after a cardiac arrest or acute distress.
Objectives: We seek to determine the occurrence of advanced medical gestures (such as resuscitation or invasive ventilation). We aim to establish whether caregiver's practices are associated with patient's age in the out-of-hospital setting. We defined the survival according to age. We also looked at the rate of hospitalizations in the intensive care unit and if age is a limitation factor.
Methods: Retrospective analysis, describing the activities of the out-of-hospital medical teams of the canton of Vaud in Switzerland, between 2005 and 2013. We worked on a database of prospectively collected data by each physician in charge of a mission along the years, and stored in the Institute of social and preventive medicine of Lausanne (IUMSP). The dependent variable was having an advanced medical gesture, yes or no. Therefore, we used logistic regression analysis to determine whether the probability of having an invasive medical gesture decreases with patient's age.
Results: We found overall that there was no significant difference between the age classes in the probability of having an advanced medical gesture except for the two last deciles of age, where there was a significant decrease of advanced medical gestures. . Survival for all causes of death at 48 hours depended on age in this study. We found that the admission in ICU was not related to age.
Conclusion: To improve the management, and help the caregivers in taking important decisions, it would be beneficial to know what exactly influences the survival and the prognosis. In this study, we found that the advanced medical gestures were not influenced by patient's age until the very old ages. It would be necessary to make a prospective study, or a qualitative one, in which the supplemental information necessary to make a causal analysis would be collected.

P341 Use of Electronic Health Record (EHR) in the consultation: the impact of a training intervention on physician-patient interactions

Cédric Lanier[1], Melissa Dominicé Dao[1], Bernard Cerutti[2], Patricia Hudelson[1], Noëlle Junod Perron[1]
[1]Geneva University Hospitals, [2]Geneva Faculty of Medicine, Genève, Switzerland

Introduction: Electronic health records (EHR) are now widely used in outpatient medical settings. Although the first minutes of the consultation are considered essential to establish a good physician-patient relationship, little is known about how doctors use EHR while initiating the consultation. The aim of the study was first to evaluate EHR use in terms of physician-patient interaction and second to assess the impact of training on how to use computer/EHR during clinical encounters during the first 10 minutes of the consultation.
Methods: A pre-post study was conducted at the Division of primary care of the Geneva University

Hospitals. 24 residents were invited to take part in a 3-month training program focusing on how to use computer/EHR during clinical encounters. The intervention included two group training sessions and 2-4 individual supervisions based on residents' own videotaped encounters. Residents were asked to videotape 3-4 encounters before and after the intervention. Outcomes measures were objective analysis of computer use with or without eye gazing or verbal interaction in relationship with the content of the interaction (using the Roter interaction analysis system).
Results: 17 residents took part in the study (61% female). Before the intervention, the first 10 minutes of the physician-patient interaction included the following contents: 29% emotional, 17% medical, 11% therapeutic and 6.6% psychosocial. Residents used the EHR more often with new patients than in follow-up encounters (31.5% vs 25.7% $p < 0.0001$). The time spent using EHR during each type of discourse was: 29.8% medical, 26.6% therapeutic, 24.5% psychosocial and 21.1% emotional. After the intervention, the overall proportion of time using EHRs decreased significantly (53.2 vs 49.8% $p < 0.0001$) and more specifically during psychosocial discourse (24.5% vs 9.76% $p< 0.0001$). These changes occurred both with or without eye gazing or verbal interaction.
Conclusion: Residents use the EHR between 20 and 30% of the time during the first 10 minutes of consultation. The intervention had a positive impact on physician-patient relationship since it reduced residents' use of EHR during sensitive issues such as psychosocial discourse.

P342 Azathioprine-induced drug fever in a patient with autoimmune hepatitis: could the dosing-related temperature profile help with a difficult diagnosis?

Stojan Todorov[1], Christian Chuard[1], Philippe Stadler[1], Daniel Betticher[1], Daniel Hayoz[1], Jürgen Bohlender[1,2]
[1]Clinique de Médecine, Hôpital Fribourgeois, Fribourg, [2]Department of Nephrology and Clinical Pharmacology, Inselspital, University of Bern, Bern, Switzerland

Introduction: Azathioprine is an immunosuppressive drug widely used to treat autoimmune diseases, chronic inflammatory conditions and to prevent rejection of transplanted organs. Drug-induced fever is a rare side-effect of azathioprine and may be easily confounded with fever of bacterial or viral origin. It is therefore a challenging diagnosis that is usually made only by way of exclusion after exhaustive clinical investigations. Its characteristics are not well known and there are no diagnostic guidelines.
Case presentation: A 62-year-old diabetic female patient diagnosed with biopsy-proven anti-actin antibody-positive autoimmune hepatitis type 1 and treated for 4 weeks with azathioprine (150 mg/d) and budesonide (9 mg/d) presented to our hospital's emergency room with fatigue and sudden onset of fever. Clinical examination showed tachycardia and arterial hypotension without significant other abnormalities. Laboratory investigations showed an elevated serum C-reactive protein (CRP, 91 mg/l) without leukocytosis or eosinophilia and an abnormal urinary sediment suggestive of urinary sepsis. She was admitted to the intensive care unit. Azathioprine and budesonide were stopped and iv antibiotics and fluids were given with rapid recovery. When azathioprine was started again at a morning dose of 75 mg/d given at 8 AM, daily fever (>38.0°C) re-occurred as a single temperature peak 6-8 h after drug intake accompanied by oppressive chest pain and persistently elevated CRP (66-80 mg/l). The patient was otherwise afebrile and asymptomatic. Extensive workup including a thoraco-abdominal CT-scan, repeated urine and blood cultures, and transthoracic echocardiography revealed no source of infection. Azathioprine-induced fever was suspected and the drug was stopped. The fever disappeared and CRP fell to 21 mg/l within 2 days. A subsequent drug re-exposure with a single morning dose consented by the patient resulted in a predictable single fever peak 8 h later with chest discomfort and an increased CRP (55 mg/l) as observed before. A serum CRP control was normal 1 week thereafter.
Conclusion: The predictable fever 6-8h after drug intake suggested an association with the delayed appearance of azathioprine metabolites stimulating cytokine production. This unique time-pattern could help identify azathioprine-induced fever and warrants investigations in similar cases to establish its potential value as a diagnostic criterion.

P343 Perception of hospital autopsies by relatives of polymorbid patients: first results of a representative survey

Iljas Rosenberg, Burkhard Gierer, Renata Flury, Peter E. Ballmer
Department of Medicine, Kantonsspital Winterthur, Winterthur, Switzerland

Background: The autopsy rates have been declining for decades throughout the world although autopsy is an important tool in the management of patients. Various factors have been discussed as a cause of this decline, e.g. technological advance in radiologic imaging, clinicians' belief in the diminished value of the autopsy, or the appalling attitude of the population towards autopsy. The attitude of the patient's relatives towards performing an autopsy has so far hardly been investigated. With the present study, therefore, we investigated the attitude of polymorbid patients and their relatives towards autopsy and whether there is a discrepancy between the patient and the relatives.
Methods: Two structured questionnaires were developed to investigate the attitudes towards autopsy of polymorbid patients (defined as patients with either a metastatic cancer or one active main diagnosis and 2 or more active secondary diagnoses) and of their relatives. These questionnaires were divided into 2 parts and answered independently. The first part contains general informations about age, sex, nationality, religion and education of the patients. In the second part, we developed 12 questions about the personal view of the patients in regard to the purpose, experience and acceptance of performing an autopsy.
Results: We interviewed 49 polymorbid patients with an average age of 68,8 ± 15,2 years and 36 relatives with an average age of 58,3 ± 20,6. In 13 patients, there existed no relative or could not be tracked. 44 (89,8%) patients and 27 (75%) relatives were willing to complete the survey anonymously. 43% of the responding patients and 33% of the relatives have been thinking about the procedure of an autopsy. In total, 89% of the answering patients generally accepted hospital autopsies and 75% would agree to an autopsy on their own. In comparison, 81% of the relatives accepted hospital autopsies and 74% would agree to an autopsy of their own and 62,9% would agree to an autopsy of one of their relatives.
Conclusion: In summary, our data show that the present polymorbid patients and their relatives predominantly have a positive attitude towards autopsy. However, we have found a discrepancy between the attitude to agree to an autopsy on their own and to an autopsy of a relative. Therefore, one important reason for the decline of autopsy rates might be the lack of debate about the autopsy between patients and relatives.

P344 Self-reported prevalence, localization and intensity of swallowing difficulties with medication intake in patients with systemic sclerosis - a cross-sectional cohort study

Markus Messerli[1,2], Rebecca Aschwanden[1], Michael Buslau[2], Kurt E. Hersberger[1], Isabelle Arnet[1]
[1]Pharmaceutical Care Research Group, University of Basel, Basel, [2]European Centre for the Rehabilitation of Scleroderma, Reha Rheinfelden, Rheinfelden, Switzerland

Background and objectives: When asked, ambulatory patients report in 9-27% of cases acute swallowing difficulties (SD) with medication intake.[1,2] The difficulties may affect their quality of life, hamper medication intake and thus adherence, and lead to hazardous coping strategies like modifying dosage forms. Health care professionals rarely ask patients about SD.[2] As systemic sclerosis (SSc) often involves the gastrointestinal tract, SD are assumed to frequently occur in SSc patients. We developed and validated a tool to assess SD with medication intake and present results obtained in SSc patients.
Methods: A self-report questionnaire was developed based on literature and an expert panel. It was post mailed to all SSc patients of the European Centre for the Rehabilitation of Scleroderma, Reha Rheinfelden (Switzerland) living in Switzerland, Germany and Austria. The study was approved by the local ethics commission and registered in the public database www.clinicaltrials.gov [NCT02105818].
Results: The questionnaire consists of 35 items in 5 sections: complaints (4-point likert scale), intensity (visual analogue scale), localization (picture), coping strategies (yes/no, free text) and adherence (German version of the Morisky Medication Adherence Scale-8D[3]). Of the 64 SSc patients enrolled in May 2014, 43 (67%) returned the questionnaire within four weeks. Prevalence of SD with medication intake was 26% (n=11), while 9 additional patients (21%) reported past SD that were overcome. Among these 20 patients, five (25%) reported strong or unbearable intensity of SD. Patients reporting SD ticked off troubles 35 times

and localized them mostly in the larynx (43%) and the esophagus (34%). Eight patients (40%) modified the dosage form. Adherence was low for 15 patients (35%) and not related to SD (p=0.222).
Discussion: Swallowing difficulties in SSc patients show a comparably high prevalence as in the general population and a wide pattern of localization and intensity. Coping strategies to overcome SD like skipping intake and splitting or crushing pills are potentially harmful. Further studies will evaluate the clinical implications of the reported SD in daily practice.
1) Marquis J, Int J Clin Pharm 2013;35:1130-6
2) Schiele JT, Eur J of Clin Pharmacol 2013;69:937-48
3) Arnet I, J Eval Clin Pract, epub 06.01.2015

Postertour 1:

Allgemeine Innere Medizin 3

Médecine interne générale 3

P345 Questioning handoffs: improve feedback and training!

Katherine Blondon[1], Rolf Wipfli[2], Christian Lovis[2], Mathieu Nendaz[1,3]
[1]Département de Médecine Interne, Réhabilitation et Gériatrie, [2]Sciences de l'Information Médicale, HUG, [3]Unité de Développement et de Recherche en Education Médicale, Faculté de Médecine, Université de Genève, Genève, Switzerland

Background: Care transitions occur between physicians during shift changes, or handoffs, and involve the transfer of role and responsibility from one person to another. Large variations exist in the handoff process. During handoffs in our General Internal Medicine (GIM) wards, day teams hand off selected patients to the next shift team. While prior handoff studies have suggested ways to standardize the content of handoffs, little evidence supports the process underlying the choice of patient cases to be discussed.
Objective: This study aims at understanding the handoff preparation process, in particular the patient selection criteria, and the verbal handoff, comparing the approaches of physician residents and supervising physicians.
Method: *W*e enrolled 12 residents and 10 supervising physicians from our GIM Department in four semi-structured focus groups. Using 8 standardized clinical vignettes, participants individually selected the patients they would hand off during a weekday evening handoff and during a weekend handoff. The reasons of their choices were discussed afterwards in the focus group to reach a consensus handoff. We coded, compared and contrasted the de-identified transcripts using thematic content analysis, focusing in particular on level of experience.
Results: On average, residents had 2.8 years of clinical experience, and supervising physicians had 6.8 years of experience. Six supervisors and three residents reported prior handoff training. The multi-rater kappa statistic showed moderate agreement for patient selection among residents and supervisors for both weekday (0.53 and 0.65 respectively) and weekend handoffs (0.44 and 0.58). Handoffs are expected to be concise, with clear day-team recommendations for anticipated problems (if-then statements), or a to-do list of tasks. To improve the continuity of care, the diagnostic reasoning should be explained, particularly for atypical situations. Patient monitoring can be improved with explicit targets and nursing staff involvement. Residents appreciated opportunities to discuss patient selection for handoffs with supervisors, and emphasized the lack of feedback on handoffs and on written summaries/progress notes.
Conclusion: Despite low formal handoff training, the participants had similar expectations of handoffs. Our findings emphasize the need for improved feedback and supervision.

P346 Advance directives and new legal rules: what do doctors and nurses know?

Tanya Balestra[1], Anneva Tozzini[1], Mattia Lepori[2]
[1]Ospedale Regionale, [2]Ente Ospedaliero Cantonale, Bellinzona, Switzerland

Background: The new Civil Code has provided for specific regulations concerning advance directives of patients since 2013. When doctors and nurses treat a patient who is incapable of making decisions, they are expected to know and strictly comply with directives previously laid down.
Aim: The aim of the study is to assess the degree of knowledge of doctors and hospital nurses about the law in force relating to advance directives.
Methodology: We carried out a written survey among 35 doctors and 35 nurses of all wards (intensive care medicine excluded) to know their degree of knowledge and their perception of the instrument of advance directives and the role of the therapeutic representative.
Results: Only 40% of doctors and 20% of nurses interviewed stated that they knew the law and its content. 30 % and 40% know it only partially, whereas 30% and 40% respectively, are totally unaware of the law. Only 40 % of doctors and 50% of nurses state that they always deal with the issue of advance directives when they take patients' medical history and 20 % and 20% respectively, do so only occasionally. 85% of the total number of respondents recognize they have some or many difficulties in talking about this issue with patients. Only 40% followed a special training on the use of advance directives and only 30% are familiar with the information documents on this subject developed by the hospital.
Conclusion: The law on advance directives is hardly known by doctors and hospital nurses. A major training and information initiative is still needed at all levels to ensure that the issue is systematically tackled within our clinical practice.

P347 Aspects influencing the decision of young internists to choose a career as a chief physician

Grischa Marti, Michael Bodmer, Drahomir Aujesky, Martin Perrig
Universitätsklinik für Allgemeine Innere Medizin, Inselspital, Bern, Switzerland

Introduction: Chief physicians are of crucial importance to ensure high quality health care in General Internal Medicine (GIM). However, a chief physician's job profile, including high duty hours and administrative tasks, may not match modern lifestyle preferences. The aim of this study was to explore aspects influencing the decision of young internists to choose the career as a chief physician. The results may be helpful for medical authorities to overcome an imminent lack of chief physicians.
Methods: Between November 2013 and January 2014, a standardized questionnaire was sent to recently certified doctors in GIM and internal medicine subspecialists. The questionnaire included questions about the general interest in becoming a chief physician, positive and negative aspects of being a chief physician (salary, prestige, responsibility, duty hours, work-life balance; leadership, administrative and non-medical tasks) and acceptable weekly working-hours.
Results: 2379 questionnaires were sent out and 1130 (47%) were returned for analyses. Overall, 47% were women, 54% worked as senior physicians and 54% worked full-time.
19% physicians were generally interested in a chief physician position. A majority of physicians perceived administrative work (85%), work-life balance (82%) and working hours (77%) as negative aspects whereas 61% perceived prestige and 60% salary as positive aspects.
52% stated that a weekly workload up to 40-60 hours would be acceptable, 25% preferred to work less than 40 hours and only 1% would work more than 80 hours per week. 41% of female and 7% of male doctors favored a job sharing model with a workload of less than 40 hours per week.
When we examined whether the amount of the salary influences the willingness to accept long working hours, 13% reported that they were willing to work more than 80 hours per week if their annual salary was above 500,000 SFr. For 70% the salary had no influence on their willingness to accept long working hours and 29% responded that they would not accept working hours beyond 60 hours per week, irrespective of the salary amount.
Conclusion: Our data show that the majority of young internists perceived work-life-balance, administrative work and high working hours as arguments against a career as a chief physician. The amount of salary had

very limited impact on physicians willingness to accept long working hours. Innovative work models may be important for the recruitment of future chief physicians.

P348 Smartphone apps and dietary counseling: how interesting in the management of patients in primary care medicine?

Delphine Amstutz, Daniela Da Costa, Sylvie Rolet, Isabelle Golard, Yves Jackson
Geneva University Hospitals, Geneva, Switzerland

Introduction: Dietary counseling represents a cornerstone in chronic diseases collaborative management in primary care. Smartphone applications (apps) provide easily accessible health information tools. They could improve self-monitoring in obese patients. Yet, their potential as tools in dietary counseling has been poorly investigated so far.
We aimed at evaluating patients'use of and interest in apps related to diet, physical activity and weight management and to analyze the quality of some apps.
Method: All patients attending the dietary consultation of the Division of primary care medicine were proposed to respond to a questionnaire from July to August 2014 with the help of translators when necessary. 21 nutrition, weight management and physical activity apps were randomly selected and analyzed according to the following criteria: accuracy of information, usability, relevance and individualization.
Results: We included 76 patients (77.6% female) aged 46 (22-70) originating from South America (n=43), Africa (n=12), Asia (n=8) and Europe (n=10).
Dietary counseling referal reasons were obesity (n=49), diabetes (n=12) and cardiovascular disease (n=12). 88% were overweight or obese.
36 (47%) owned a smartphone and 6 (8%) had used > 1 app related to nutrition, physical activity or weight management.
Among those having a smartphone, 26 (72%) declared interest in using such apps for health reasons.
Most apps analyzed have important limitations: unclear information, guilt-inducing messages and unrealistic promises through pictures and texts focused on weight, which could induce or reinforce eating disorders. Moreover, a lack of individualization regarding socio-cultural context and dietary habits could be a barrier to lifestyle change.
Discussion: Apps were perceived as interesting sources of health information by most patients with chronic diseases owning a smartphone and seen at a dietary consultation in primary care setting. However, apps quality varies greatly and requires careful selection and counseling prior to use by health professionals.
Conclusion: Considering patients' interest and the potential for quality improvement, there is a need to develop scientifically sound apps and to test them in the management of chronic diseases in primary care.

P349 Statin-induced rhabdomyolysis - a small tablet with a fatal effect

Eva Naegeli[1], Reinhard Imoberdorf[1], Florian Kuss[1], Martina Jäggi[2], Jaques Gubler[3]
[1]Innere Medizin, [2]Zentrum für Intensivmedizin, [3]Medizinische Poliklinik, Kantonsspital Winterthur, Winterthur, Switzerland

Introduction: Large, placebo-controlled studies have provided evidence that statins can substantially reduce the incidence of heart attacks. No drug is without adverse effect potential. By interfering with the synthesis of coenzyme Q10, statin-induced muscle damage may be far more common than that previously thought. Muscle side effects extent from myalgia to life-threatening rhabdomyolysis. Here, we report on a patient with a life-threatening serious adverse statin event.
Case: A 66 years old patient was admitted to our hospital for presumed pneumonia with fever, dyspnoea and weakness. He had a known chronic obstructive lung disease and was taking 40mg /d of Simvastatin as primary prophylaxis. On admission, the patient was obtunded, tachypnoic, had a temperature of 36.3°C, a blood pressure of 168/88 mmHg and had to be intubated and mechanically ventilated shortly thereafter. His abnormal laboratory values included an elevated creatine kinase (CK) of 1474 U/L (N < 180 U/L), so the

statin was immediately stopped. Initially there was a reduction of the CK, but a few days later it rose again in parallel to a rapid decrease of the kidney function and development of tetraparesis. The clinical course was nevertheless complicated by a severe rhabdomyolysis, with acute kidney injury, dyskinesias and tetraparesis, necessitating longterm artificial ventilation. The immunologic testing showed no evidence for a rheumatologic cause. A biopsy of the M. vastus lateralis revealed necrotic fibers, denervation and less "ragged red fibers" with little inflammation. The anti-HMGCR (3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase) antibodies were negative.
Discussion: Myopathy, a known dose dependent side effect of statins, is rare in randomized controlled trials, but less so in observational studies and clinical experience. Even though the anti-HMGCR antibodies were negative, we postulate a statin-induced autoimmune necrotizing myopathy with rhabdomyolysis. Our case is a striking example of collateral damage of prophylactic therapy.
Conclusion: The side effects of statins for the individual patient can have serious consequences and should be carefully considered.

P350 Feasibility and effectiveness of dancing classes for depressed or isolated diabetic patients

Olivia Braillard, Mélissa Dominicé Dao, Patricia Hudelson Perneger, Mélinée Schindler, Noëlle Junod Perron
Département de Médecine Communautaire, de Premier Recours et des Urgences, Hôpitaux Universitaires de Genève, Genève, Switzerland

Introduction: « Dancing Communities » is a dancing classroom created by Pierre Dulaine whose original objective was to help people break down social barriers, learn about respect, communicate and improve self-confidence. This program is now being offered to patients suffering from medical conditions with the aim of improving their mental health, general well-being and quality of life, but its impact has never been formally assessed. Our study explored the feasibility, acceptability and effectiveness in a medical environment.
Methods: We conducted a pre- post and controlled intervention study at the Geneva University Hospitals. Outpatient diabetic patients perceived by their primary care physicians or diabetes specialists to be depressed and/or isolated were invited to participate. The program consisted of 8x 90 min sessions over two months during which participants were taught several ballroom dances. Outcome measures were level of quality of life, depression and isolation (questionnaires). Perceptions and satisfaction were explored through semi-structured phone interviews.
Results: Of the 62 participants initially recruited, 39 attended at least one session and 30 attended 4 or more sessions. Semi-structured interviews revealed that physical limitations of patients were largely underestimated. While most participants said the course had a positive impact on their emotions, self-image and self-confidence, others said they disliked the physical proximity to other participants and had negative impressions of the group. Spending time with other diabetic patients and informally exchanging experiences was appreciated. However some had expected the dancing program to integrate more therapeutic educational activities.
Conclusion: A dancing program in a medical environment was well perceived by most participants. However, in order for such a program to meet chronic patient expectations, program coordinators should better assess the physical limits of participants and link dancing to therapeutic educational activities.

P351 Assessing the affective load in the narratives of women suffering from fibromyalgia: the clinicians' appraisal

Anne-Françoise Allaz[1], Elodie Girard[2], Valérie Piguet[3], Jules Desmeules[3], Christine Cedraschi[1,3]
[1]Internal Medicine & Rehabilitation, [2]Liaison Psychiatry, [3]Clinical Pharmacology & Toxicology, University Hospitals of Geneva, Geneva, Switzerland

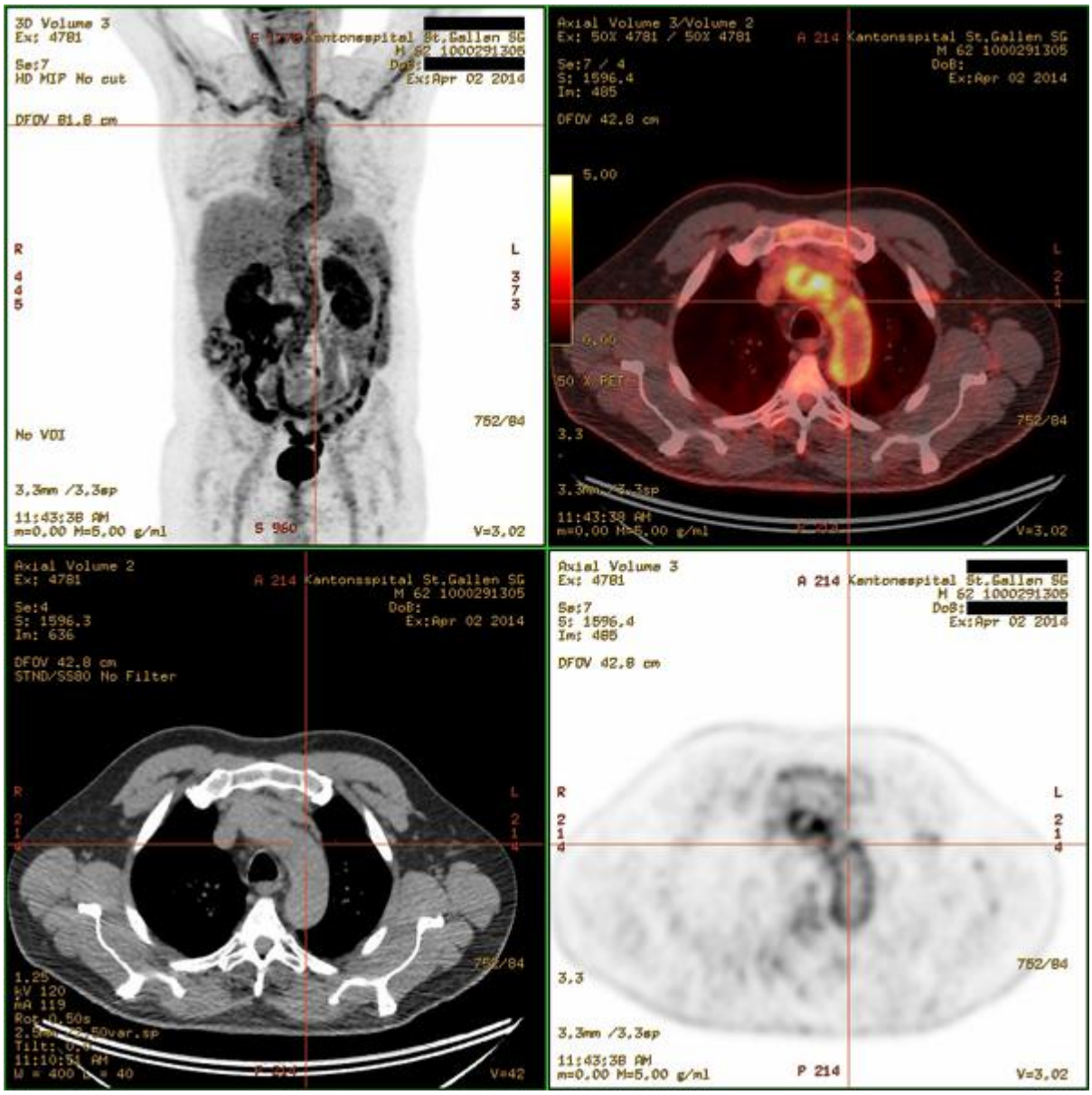
Objective: Fibromyalgia is characterized by chronic widespread pain and various associated symptoms, including psychological distress. This study presents a secondary analysis of the interviews of patients with fibromyalgia to appraise the affective load of the patient narratives as assessed by independent clinicians.

Methods: Three clinicians, an internist, a psychiatrist, and a psychologist, who were experienced in chronic pain reviewed the interview transcripts of 56 women eliciting their views regarding fibromyalgia onset. A Clinical Global Impression (CGI) scale was used (0=no affective load to 5=maximum affective load) to provide a subjective appraisal of the intensity of the affective impact, as suggested in the transcripts and from the clinician perspectives.
Results: The mean affective load was 3.6 (SD=±1), indicating the perception of a high affective load in the clinicians. Values indicating a high or very high affective load (≥4 points on the CGI scale) were more frequent than those in the lower range (23 narratives (41%) vs. 3 (5%)). The inter-rater agreement of the affective load of the narratives was high (K>.85). These results of the clinician perspectives parallel those of the patient narratives, emphasizing disruptive circumstances, psychological distress and hopelessness surrounding symptom onset.
Conclusion: The affective load in the narratives of these patients with fibromyalgia was high and had a negative undertone when considered from the clinicians' perspective. This study highlights the importance of considering the affective resonance in the context of therapeutic relationships that are often emotionally laden and highly challenging for the clinician.

P352 Case report: a rare concomitant of large vessel vasculitis

Michael Dicker[1], Tino Schneider[2], Gediminas Matulis[3], Markus Diethelm[4]
[1]Klinik für Neurologie, [2]Klinik für Pneumologie/Schlafmedizin, [3]Klinik für Rheumatologie, [4]Klinik für Allgemeine Innere Medizin und Hausarztmedizin, Kantonsspital St. Gallen, St. Gallen, Switzerland

A 62 year old male patient with history of cough and B-symptoms was admitted to our hospital for further diagnostics. He suffered of a dry, exercise induced cough for 3 months and subfebrile temperature, weight loss and night sweats for 6 weeks despite no other symptoms. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were raised. Beforehand an abdominal sonography and a CT scan of the thorax were normal, an empiric antibiotic therapy initiated by his general practitioner showed no success. Prior to the admission to our hospital extensive diagnostics were performed in an external hospital. Despite a detailed anamnesis no further trendsetting symptoms were found. A thorough clinical examination revealed no relevant abnormalities. A complete blood count, an urinalysis and serum chemistry were done without new relevant pathologic results. Blood cultures were repeatedly negative. Serologic testing for rheumatic (ANA, rheumatic factor, ANCA, SS-A, SS-B) and infectious diseases (brucellosis, tularemia, Q fever, HIV, coxiella burnetti and bordetella pertussis) was normal. Protein electrophoresis and testing for light chains also showed no abnormalities. Transthoracal and transesophageal echocardiography revealed no hints for endocarditis or an atrial myxoma. An abdominal CT scan was also normal.
For more diagnostics and especially a bronchoscopy the patient was transferred to our hospital. Lung function testing was normal despite a raised exhaled nitrite oxide. Methacholine challenge test was normal. Despite these normal results and also a normal CT scan of the thorax (also no ground glass opacities) a decision was made to perform a bronchoscopy with a bronchoalveolar lavage (BAL). The BAL revealed a lymphocytic alveolitis. At last we performed a PET-CT scan which showed large-vessel inflammation of the whole aorta and its primary branches. Neither involvement of temporal artery nor a focus suspicious of an infection or malignoma was seen.



[PET-CT_scan]

MR angiography showed no stenosis of the involved vessels. With this diagnosis of a primary large vessel vasculitis we started high dose steroids, methotrexate and aspirin. Follow-up visits showed good response to this treatment.

Conclusions: Lymphocytic alveolitis is described in literature as a rare concomitant in large vessel vasculitis. PET-CT scan can be a helpful tool in cases of fever of unknown origin.

Postertour 1

Allgemeine Innere Medizin 4

Médecine interne générale 4

P353 Electronic health record implementation reconsidered: a poor surrogate for health IT adoption in Swiss ambulatory care

Sima Djalali, Nadine Ursprung, Thomas Rosemann, Oliver Senn, Ryan Tandjung
Institut für Hausarztmedizin, Universität Zürich, Zürich, Switzerland

Background: The successful implementation of health information technology (IT) is most often measured by the adoption rate of electronic health records (EHR). However, this approach denies that the variety of EHR definitions and applications in use limit the validity of this surrogate outcome.
Objective: We aim to provide a detailed overview over the implementation of health IT in Swiss ambulatory care by stepwise assessing how medical patient information is usually received, processed and transferred and identify barriers towards physicians' use of structured electronic data exchange.
Methods: Between May and July 2013, we conducted a cross-sectional survey of 1200 practice based physicians in Switzerland. Participants were asked to report on their technical means and where applicable their paper-based workarounds to process laboratory data, examination results, referral letters and physicians' letters. Physicians view of barriers towards health IT use was determined by an attitude sum score.
Results: The response rate was 57.1% (n=685). The sample was considered to be representative for physicians in Swiss ambulatory care. 35.2% of the participants used an EHR as a longitudinal electronic record of patients' health status generated by one or more encounters in the practice. Thereof < 40% used electronic laboratory order systems. 31−75% (depending on laboratory test) received laboratory results as structured electronic data. < 50% received examination results as structured electronic data or electronic document, respectively. 52.3% dispatched referrals to other physicians occasionally (median 20% of all referrals) via e-mail. A positive scoring on the attitude sum scale had moderate impact on EHR adoption (OR 1.30, CI 1.24−1.37) and the use of health IT processing laboratory data, examination results, referral letters and physicians' letters (OR 1.04−1.1, all $p < 0.05$).
Conclusion: Although the one third of Swiss physicians records patients' health status with the help of software, the extent of health IT implementation varies with only a small minority of physicians realizing a seamless exchange of medical data. Paper-based workarounds concern individual tasks within a workflow and occur particularly when data need to be converted or transferred. In the absence of regulatory obligations or incentives, physicians' individual attitude towards health IT had only minor impact upon the use behavior or behavioral intention of physicians.

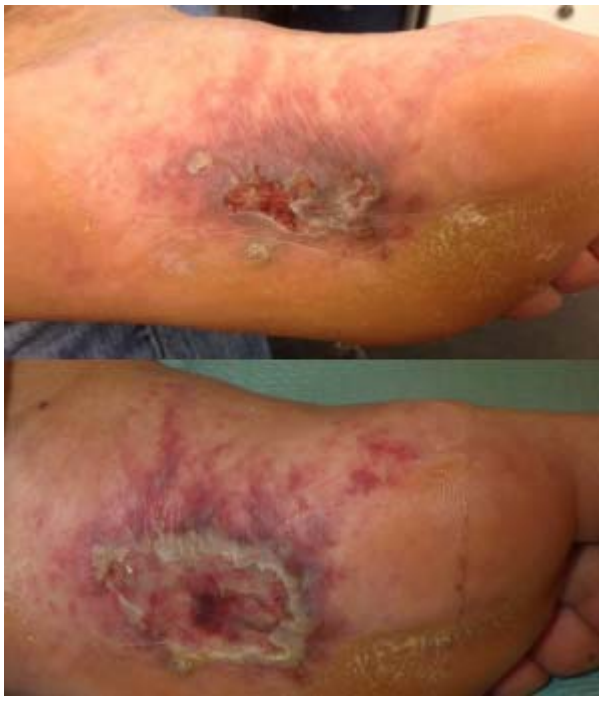
P354 Eine ungewöhnliche Ursache eines Ulcus im Fussgewölbe

Corinne Furrer, Patrick Hakman, Philippe Rochat, Beat Bundi, Beat Frauchiger
Innere Medizin, Kantonsspital Frauenfeld, Frauenfeld, Switzerland

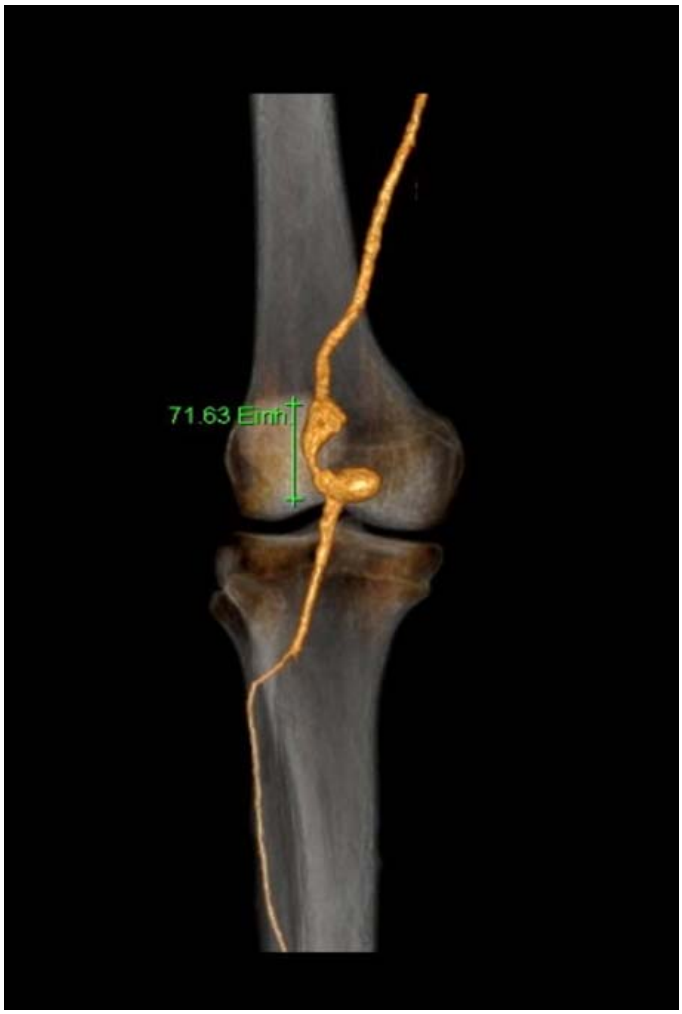
Einleitung: Ulcera der Füsse sind oft differentialdiagnostische Herausforderungen. Wir berichten nachfolgend über ein Ulcus im Fussgewölbe, bei dem schliesslich eine nicht-alltägliche vaskuläre Ursache gefunden wurde.
Fallbeschreibung: Ein 60-jähriger Patient mit kardiovaskulären Risikofaktoren (arterielle Hypertonie und Nikotinabusus) wurde zugewiesen bei akuter Manifestation einer schmerzhaften und grössenprogredienten oberflächlichen Hautläsion an der linken Fusssohle mit dem Bild eines plantaren Ulcus mit livedoartiger Umgebung (Abb. 1), aufgetreten nach einem längeren Spaziergang. Der Puls über der A. poplitea war links verbreitert und kräftiger palpabel als rechts. Die Pulse über der A. tibialis anterior und A. tibialis posterior waren regelrecht palpabel. Laborchemisch ergaben sich keine wegweisenden Befunde. Eine Polyneuropathie konnte nicht gefunden werden. In der Kultur vom Wundabstrich bestand kein Bakterienwachstum, die Biopsie zeigte Ulcusgewebe mit diskreten vaskulitischen Veränderungen der kleinen bis mittelgrossen

Gefässe, trotz fehlender Eosinophilie im Blut am ehesten durch Cholesterinembolien bedingt. Diverse Abklärungen (u.a. ANA, ANCA, Rheumafaktoren, Kälteagglutinin- und Anti-Phospholipid-AK, Protein C und -S) fielen unauffällig aus.

In der Proteinelektrophorese präsentierte sich das Bild einer akuten Entzündung.
Im MRI des Fusses ergaben sich keine Hinweise für eine Fasziitis. Die Duplexsonographie und CT-Angiographie (Abb. 2) führten schliesslich zum Befund eines ca. 7,2 x 2,4 cm grossen teilthrombosierten Poplitealaneurysmas (PAA) links. Trotz der atypischen Lokalisation mussten wir somit eine ischämische Genese des Ulkus bei rezidivierenden arterio-arteriellen Embolien, ausgehend von einem PAA, annehmen. Therapeutisch wurde eine orale Antikoagulation mit Marcoumar begonnen, überlappend mit Heparin in therapeutischer Dosis. Das Ulcus zeigte nun unter lokaler Wundpflege eine gute Heilungstendenz. Eine operative Versorgung des PAA mittels femoro-poplitealem Bypass wurde geplant.
Schlussfolgerung: In den meisten Fällen finden sich die Nekrosen bei arterio-arteriellen Embolien in der Endstrombahn, am häufigsten in den Zehen. Der vorliegende Fall zeigt, dass selten auch Embolien in die Fusssohle möglich sind und als Differentialdiagnose bei plantaren Ulcera in Betracht gezogen werden müssen. Dabei ist das PAA eine mögliche Emboliequelle, die insbesondere bei deutlich verbreiterten Poplitealpulsen rasch gesucht werden muss.



[Abb. 1_Fussgewölbe links]



[Abb. 2_Knieregion links von hinten]

P355 Diagnostic errors in medicine - a clinical case

Claudia Buser, Andriyana Bankova
Luzerner Kantonsspital, Luzern, Switzerland

Introduction: Medical diagnosis is a process susceptible to diagnostic errors defined as wrong, delayed or missed diagnosis. There are 3 causes for diagnostic errors: „no fault", system-related and cognitive causes. Cognitive errors, which are the most common type of diagnostic errors, are the result of defective clinical reasoning due to heuristic pitfalls and biases.
Case report: A 57 year old woman was admitted to the hospital with right-sided pleuritic pain, dyspnea, hemoptysis and fever for 8 days and weight loss of 3 kilograms in the last few months. Medical history revealed exposure to tuberculosis. Clinical examination was normal except for subfebrile temperature and decreased breath sounds in the right lower lobe. Abnormal laboratory findings included leukocytosis (14.5 G/L), elevated C-reactive protein (180 mg/L) and D-dimer (45900 ng/ml). Sputum cultures for acid-fast bacilli were negative. The initial interpretation of the chest computed tomography revealed consolidation in the left inferior lobe with bilateral hilar lymphadenopathy and pulmonary infiltrate in the right inferior lobe with concomitant pleural effusion. Bronchoscopy demonstrated alveolar hemorrhage in the right inferior lobe, therefore prophylaxis with dalteparin was discontinued. Systemic vasculitis was serologically ruled out. The medical condition of the patient was complicated by deep vein thrombosis of the right leg and therefore anticoagulation was initiated. Computed tomography-guided puncture of the consolidation in the left inferior lobe showed histological middle-grade differentiated adenocarcinoma of the lung. The diagnosis of non-small-cell lung carcinoma (NSCLC) T2aN3M0 with paraneoplastic thromboembolic syndrome was made. Palliative chemotherapy with Carboplatin and Pemetrexed (Alimta®) was started. In retrospect the initial

interpretation of the chest computed tomography missed right-sided pulmonary embolism. The histological result however led to revision of the medical case and explanation of the symptoms of the patient at time of admission.
Conclusion: In this clinical case a system-related error (insufficient interpretation of chest computed tomography) was associated with premature conclusion and thus delayed anticoagulation. On the other hand the diagnostic process was influenced by additional and misleading information (tuberculosis exposure, alveolar hemorrhage), contributing to delayed diagnosis.

P356 Autoimmune encephalitis leading to cancer diagnosis

Marie-Elisabeth Kajdi[1], Angela Mirjam Fischer Maranta[1], Olav Rychter[1], Raphael Jeker[1], Paolo Glisenti[2], Thomas Fehr[1]
[1]Department für Medizin, Kantonsspital Graubünden, Chur, [2]Department für Medizin, Spital Oberengadin, Samedan, Switzerland

Objective: To describe clinical and immunologic features of patients presenting with neuropsychiatric symptoms of unclear origin finally being diagnosed as paraneoplastic autoimmune encephalitis (AE).
Background: AE, initially classified as limbic encephalitis, was first described in 1960. Since then, an increasing number of "idiopathic" seizures and encephalitides have been identified as autoimmune-mediated. AE describes heterogeneous neurological disorders with subacute onset of mnestic deficits, cognitive dysfunction, seizures and psychiatric symptoms. The term „limbic" might be misleading as affected brain areas extend the limbic system. Targets of autoantibodies can be subdivided in neuropil and neuronal cell-surface receptors. Diagnosis of AE is difficult due to the very broad differential, including rheumatic, infectious, psychiatric and neurodegenerative diseases.
Methods: We retrospectively reviewed the charts of three consecutive cases with AE focussing on onset and type of symptoms, diagnostic measures and laboratory findings leading to diagnosis.
Results: Three patients (2 women, 1 man), aged 66 to 83 years, presented with subacute onset of neuropsychiatric symptoms ranging from depression and vertigo to complex seizures and short term memory dysfunction. During their clinical course, all patients underwent lumbar punction and imaging studies of the brain. Regarding cerebrospinal fluid examination an unspecific inflammatory state with pleocytosis, elevated proteins, intrathecal IgG synthesis and oligoclonal bands was found (n=3). Magnetic resonance imaging (MRI) was performed in 2 patients: one showed subcortical and left temporal lobe lesions. In all 3 patients neuro-autoantibodies (Anti-Yo, Anti-Ri, Anti-GABA(B)) were detected in the serum, which led to diagnosis of AE and cancer: 2 patients had a tumor history and developed recurrence; in 1 patient neurological symptoms preceded diagnosis of an underlying cancer. Two of our patients were initially wrongly diagnosed with depression (n=1) or syncope due to arrhythmias (n=1) leading to delay of appropriate therapy and tumor search. Time between onset of symptoms and diagnosis ranged between 0.5 an 12 months.
Conclusion: AE is an important differential diagnosis of cognitive dysfunction. Diagnostic tools such as autoantibody detection should be used more frequently and, if positive, prompt search for cancer.

P357 Referral rates in Swiss primary care with a special emphasize on reasons for encounter

Ryan Tandjung[1], Andreas Hanhart[2], Fredi Bärtschi[3], Thomas Rosemann[1], Oliver Senn[1]
[1]Institut für Hausarztmedizin, Universität Zürich, Zürich, [2]Bachtelpraxis, Wetzikon, [3]Gemeinschaftspraxis Lupfig, Lupfig, Switzerland

Background: Referrals from primary to secondary care are crucial decisions with major impact on quality of care and costs. Most referral rates in earlier studies were based on the number of consultations rather than on the number of reason for encounters (RFE). The aim of the current study was to update data on consultations, RFE and referrals in Swiss primary care.
Methods: Primary care physicians (PCPs) collected data on consultations on fifteen different days in three non-consecutive months in 2012/2013. PCPs collected demographic data of patients and up to six RFE per

consultation. For each RFE the PCP had to indicate whether a referral was initiated. The RFE were coded according to the international classification of primary care (ICPC2).
Results: 90 PCPs (18.9% females) with a mean practice experience of 17.3 (SD 9.3) years participated in our study. 24'774 consultations were recorded, corresponding to 42'890 RFE, resulting in 1.73 (SD 1.07) RFE per consultation. 2427 RFE (of 2341 consultations) led to a referral, corresponding to a referral rate (RR) of 9.44% (95%-CI 9.08-9.81%) based on consultations and 5.65% (95%-CI 5.43-5.87%) based on the number of RFE. Frequency of RFEs according to ICPC chapters was inversely correlated with the RR.
Conclusion: The broad spectrum of problems presented in primary care and an average of 1.7 RFE per consultation indicates the complexity of primary care consultations, nevertheless 94.3% of all problems brought into in these consultations were handled and solved in primary care. This figure clearly reflects the crucial role of the PCPs as a coordinator of healthcare.

P358 Clinical manifestations of baclofen intoxication in patients with alcohol dependence: three case reports

Thierry Favrod-Coune[1], Anne François[1], Fréderic Guillo[2], Barbara Broers[1]
[1]Service de Médecine de Premier Recours, [2]Direction Générale des Soins, Geneva University Hospitals, Genève, Switzerland

Introduction: Baclofen is a GABA-$_B$ receptor agonist, used for spasticity (max dosage around 80 mg/day). A few studies suggest an interest for the use of high-dose baclofen in the treatment of alcohol dependence, but evidence from large RCT is lacking. Still, in France, a "recommendation for temporary use" was given in March 2014. In Switzerland, mostly the Romandie, off-label prescription of baclofen exists. Nourished by media reports, some patients will try out high doses of baclofen in order to become "indifferent" towards alcohol. Side-effects of sleepiness and dizziness are common, but we were confronted in the Geneva University Hospital with other presentations of baclofene intoxication.
Method: Three case reports.
Results: The first patient, with addiction to alcohol and cocaine, raised baclofen doses slowly (5mg 3 x/d every 3 days). At dose 210 mg/day, he developed anxiety and drowsiness, and consumed alcohol and cocaine. He then felt strange, confuse, impulsive and deliberately had sexual relation with a person known to have HIV. He contracted HIV and attributed his behavior to the baclofen, and interrupted the treatment.
The second case, known for depression and alcohol dependence, presented with symptoms compatible with stimulant intoxication. She had raised the baclofen doses without respecting the prescription up to 150 mg in 1 week. She presented with insomnia, nightmares, anxiety, dry cough and chest oppression. Clinical examination showed elevated body temperature (37.9°C), psychomotor agitation, tremulations, tachycardia and mild hypertension. Paraclinical tests were normal except neutrophilia (9.22 G/L without left shift) and C reactive protein (106 mg/L). She continued with the same doses and side effects disappeared spontaneously.
The third patient raised baclofen to 120 mg per day in 2 and half months. At that dose she experienced a pre-syncope, dizziness and anxiety that disappeared after treatment interruption.
Conclusion: Patients with alcohol dependence might wish to try baclofen, considered sometimes as a miracle therapy. Even if for some patients this medication, if integrated in a global therapy, might be beneficial, side-effects of baclofen can be important and even life-threatening, especially if taken with alcohol or other substances. Patients and physicians should be aware of these risks. In case of intoxication, baclofen should be stopped until the appearance of withdrawal symptoms, and then gradually tapered.

P359 Mykoplasmenpneumonie - nicht immer harmlos

Tiziana Straessle, Annekathrin Mehlig, Bernhard Kessler
Medizinische Universitätsklinik, Kantonsspital Baselland, Liestal, Switzerland

Hintergrund: *Mycoplasma pneumonia* ist eine der häufigsten Ursachen für ambulant erworbene Pneumonien. Mykoplasmen sind extra- und intrazellulär lebende Bakterien ohne Zellwand und werden durch Tröpfcheninfektion von Mensch zu Mensch übertragen. Viele durch *Mycoplasma pneumonia* verursachte Infekte verlaufen asymptomatisch. Es gibt jedoch auch schwere Verläufe.
Klinischer Fall: Ein 45-jähriger Landwirt wurde wegen eines Infekts der unteren Atemwege mit Fieber und Husten für sechs Tage mit Amoxicillin/Clavulansäure per os behandelt und bei fehlender Besserung und zunehmend Dyspnoe hospitalisiert. Bei Eintritt war der Patient tachypnoeisch mit einer peripheren Sauerstoffsättigung von 89%, subfebril (37.9°C), hatte ein makulöses Erythem am Oberkörper, auskultatorisch Rasselgeräusche links basal sowie Giemen und Pfeifen über allen Lungenfeldern. Leukozyen (11.9×10^9/l) und CRP (129 mg/l) waren erhöht, das Procalcitonin negativ. Im Röntgenbild des Thorax zeigte sich ein flächig konfluierendes pneumonisches Infiltrat im posterioren Oberlappensegment links. Bei atypischer Pneumonie mit respiratorischer Partialinsuffizienz wurde der Patient auf die Intensivstation aufgenommen und eine antibiotische Therapie mit Cefepim intravenös und Levofloxacin per os begonnen. Bei positiver *Mycoplasma pneumonia* - PCR aus dem Nasopharyngealsekret wurde eine Mykoplasmenpneumonie diagnostiziert und die antibiotische Therapie mit Levofloxacin als Monotherapie weitergeführt. Der Patient benötigte während acht Tagen eine Nasal High-Flow Therapie (NHFT), um eine adäquate Oxygenierung sicherzustellen. Hiermit konnte letztlich die drohende Intubation vermieden werden. Ein Weaning von der NHFT war nur zögerlich möglich, so dass der Patient erst nach zehn Tagen intensivmedizinischer Therapie stabil auf Normalstation verlegt werden konnte. Der Austritt nach Hause erfolgte am Tag 18. Die im gleichen Haushalt lebende Mutter und der Bruder wurden eine Woche später ebenfalls wegen respiratorischen Infekten hospitalisiert. Bei beiden wurden *Mycoplasma pneumonia* nachgewiesen.
Klinische Relevanz: Bei schweren Pneumonien sollten atypische Erreger in der Wahl der empirischen Therapie berücksichtigt werden, insbesondere wenn eine Verschlechterung unter Beta-Laktam-Antibiotika eintritt. Extrapulmonale Manifestationen wie Erytheme oder epidemiologische Hinweise mit gehäuftem Auftreten von respiratorischen Infekten innerhalb einer Familie können auf Mykoplasmen hindeuten.

Postertour 2

Allgemeine Innere Medizin 5

Médecine interne générale 5

P360 The pain network of the Geneva University Hospitals

Christophe Luthy[1], Sarah Kupferschmid[2], Valérie Piguet[3], Sandra Merkli[4]
[1]Internal Medicine & Rehabilitation, [2]University Hospitals of Geneva, Geneva, [3]Clinical Pharmacology & Toxicology, Geneva University Hospitals, Genève, [4]Internal Medicine, University Hospitals of Geneva, Geneva, Switzerland

Introduction: The prevalence of pain among hospitalized patients ranges from 40% to 80%. Pain is a significant source of dissatisfaction and interferes with normal activities and interpersonal relationships; it is also associated with increased medical complications. Quality improvement collaboratives offer promising perspectives to enhance pain management at an institutional level. The Pain Network of the Geneva University Hospitals (HUG) is an opportunity to attest the feasibility and effectiveness of such strategies.
Method: This Network was launched in 2003. During the past 12 years, the program used multifaceted interventions which included staff and patient education, audit and feedback as well as opinion leaders. The Network implemented:
1) validated pain measurement tools,
2) guidelines and information documents on diagnosis and treatment,
3) standards for the use of patient-controlled analgesia,
4) information leaflets for patients about pain and current available treatments, staff education on pain and pain management, within all departments.
Yearly meetings are organized to discuss the implemented initiatives with the various stakeholders. Structured feedback on strengths and weaknesses of these initiatives is provided by the multidisciplinary team of health professionals participating to the Network.
Results: Analysis of institutional indicators collected on a regular basis (i.e. patient satisfaction questionnaires, surveys among healthcare professionals) confirmed the benefits of our program to enhance pain assessment and pain management. The diffusion of guidelines and information documents within the HUG increased, as indicated by the higher demand made to the central store of the HUG and by the statistics of the use of a dedicated website (http://reseaudouleur.hug-ge.ch/) that provides additional information (e.g. training offers, phone numbers).
Conclusions: Quality improvement collaboratives constitute an effective approach to get better pain measurement, pain management and pain relief. This type of approach is increasingly acknowledged and the Geneva Pain Network has been awarded the Swiss Quality Award as well as the clinical prize of the Swiss Association for the Study of Pain in 2013. Further studies are needed to determine the overall cost-effectiveness of such programs.

P361 An uncommon variant of Lemierre's syndrome

Rupprecht Lange, Sebastian Wirz, Jonas Rutishauser
University Clinic of Internal Medicine, Kantonsspital Baselland, Bruderholz, Switzerland

Introduction: The genus *Fusobacterium* includes numerous species of obligately anaerobic, nonsporeforming Gram-negative rods colonizing the oral cavity and intestinal tract. Fusobacteria cause various infections including abscesses and septicemia.. Fusobacteria necrophorum has been identified most frequently as the causative germ in Lemierre's syndrome, an infection of the oropharyngeal region complicated by thrombosis of the internal jugular vein.
Patient, methods and outcome: A 60 year-old male was hospitalized due to loss of appetite, malaise, diarrhea, abdominal pain, and fever. The patient was under long-term treatment with mestinone, azathioprine, and prednisone for myasthenia gravis. On admission, blood pressure was 105/90mmHg, heart

rate 83/min, and there was epigastric pain upon palpation. CRP and leukocytes were elevated to 263mg/l and 11,5G/l, respectively. Liver enzymes were slightly above normal.
A contrast-enhanced CT scan showed partial thrombosis of the hepatic vein and a large lobulated mass in the right lobe of the liver. Blood and stool cultures were taken, and treatment with heparin and azithromycin was initiated. A repeat CT scan suggested a liver abscess, and a drain was inserted for 7 days. Blood cultures remained sterile, but cultures of hepatic pus grew *Fusobacterium nucleatum* after 4 days. Antibiotic treatment was changed to amoxicillin/clavulanate for 42 days. Colonoscopy and examination of the oral cavity were unremarkable. The patient improved gradually and was discharged after 43 days.
Conclusion: The association of liver abscess with *Fusobacterium nucleatum* and thrombosis of the hepatic vein has rarely been described (refs. 1, 2) and is reminiscent of Lemierre's syndrome. How *Fusobacteria* trigger thrombus formation is unknown.

References:

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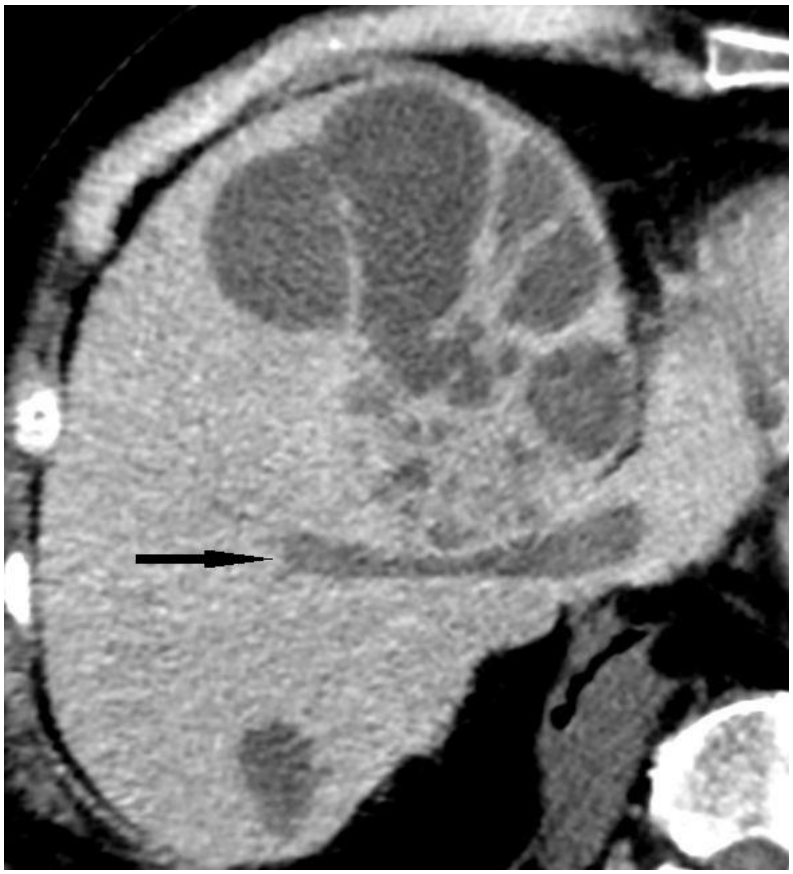
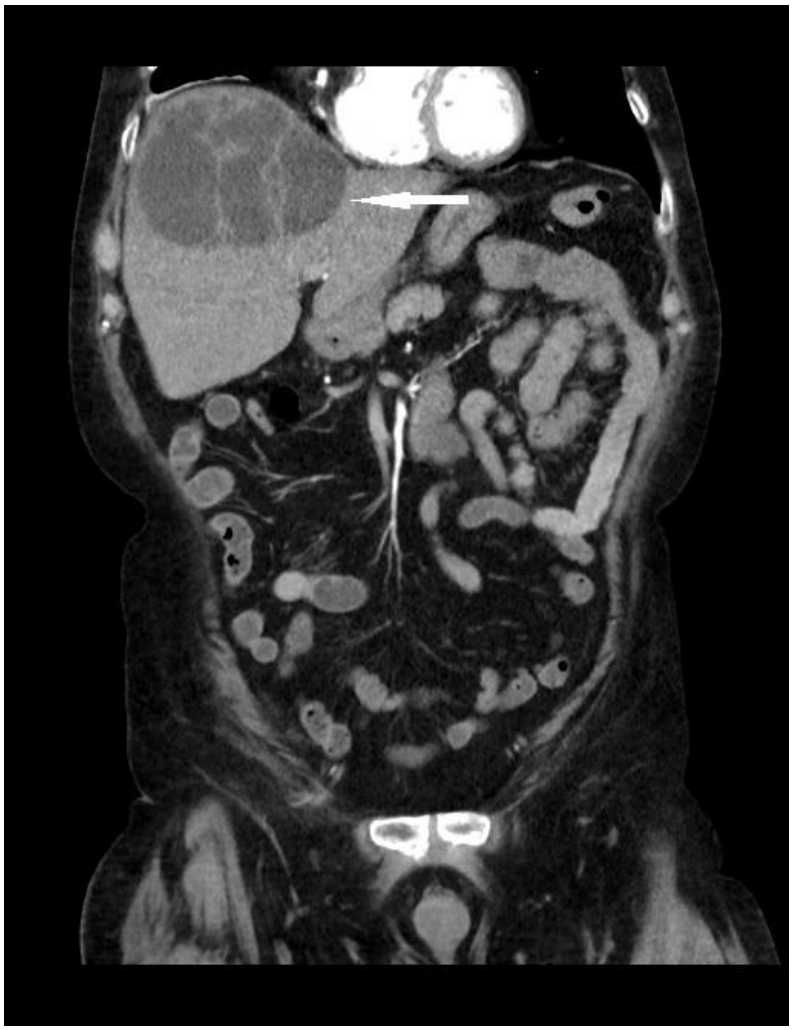


[Figure 1]



[Figure 2]

P362 Interprofessional teamwork and its impact on clinical reasoning: results of a qualitative study

Katherine Blondon[1], Virginie Muller-Juge[2], Stéphane Cullati[3], Patricia Hudelson[4], Fabienne Maître[1], Nu V. Vu[2], Georges Savoldelli[2,5], Mathieu R. Nendaz[1,2]
[1]Département de Médecine Interne, Réhabilitation et Gériatrie, HUG, [2]Unité de Développement et de Recherche en Education Médicale, Faculté de Médecine, Université de Genève, [3]Service Qualité des soins, [4]Département de Médecine Communautaire et de Premier Recours, [5]Département d'Anesthésiologie, de Pharmacologie et des Soins Intensifs, HUG, Genève, Switzerland

Context: In-patient care requires close collaboration between doctors and nurses. We aimed to study whether and how individual and teamwork characteristics contribute to diagnostic clinical reasoning and patient management in General Internal Medicine wards.
Methods: Resident-nurse team performances were observed during an urgent internal medicine high-fidelity simulation scenario. Each participant was then interviewed using stimulated recall to explore their reasoning processes and perceptions during the simulation. Using a consensus-based assessment of effectiveness and collaboration using a qualitative, grounded theory approach, three investigators (two doctors, one nurse) coded and extracted common themes, iteratively comparing and contrasting the transcribed audio and video data.
Results: The analyses of 14 resident-nurse teams suggest that both individual and teamwork characteristics can favor or hinder the effectiveness of team clinical reasoning. Nurses tended to use a physiology-based, pragmatic approach, favoring immediate management aspects, while residents used an etiological, more

abstract and global approach, favoring diagnostic workup. When nurses provided concise, complete, and relevant information at the onset, or suggested pertinent elements for diagnosis or management, the team performed better. Inadequate role perceptions (e.g., "nurses should only follow orders") hindered helpful anticipated suggestions or actions. Impeding interaction processes included low situational awareness, low mutual support, and nurse task-overload or information-overload by the resident.
Conclusion: While interpersonal approaches may differ, recurrent individual and team characteristics influence efficiency and relevance of team diagnostic clinical reasoning and patient management.

P363 What experienced experts almost miss: unusual somatic causes of fatigue

Eva Simona Laube[1], Nicole Regula Bonetti[1], Esther Bächli[2,3], Jürg Hans Beer[1,4]
[1]Internal Medicine, Cantonal Hospital of Baden, Baden, [2]Internal Medicine, Hospital of Uster, [3]President of the Swiss Society of Department Heads, Uster, [4]Laboratory for Platelet Research, Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland

Background: Fatigue as an everyday symptom of everyday patients is often considered to be of minor importance, even by experienced doctors. Managing "tired" patients can present a challenge. Often enough it is attributed to psychosomatic reasons or disregarded altogether. This may lead to underrecognition of potentially treatable somatic diseases.
Methods: To approach this complex field we asked the most experienced clinicians to share their (almost) missed somatic causes of fatigue. We reasoned that these cases would be of great teaching value. We conducted a nationwide survey among the members of the Swiss Society of Department Heads of Medicine. A questionnaire with the following inquiries was sent out to 150 chiefs:
1. What was the most surprising somatic cause of fatigue in your career thus far?
2. Which diagnosis did you (almost) miss?
Results: We received the lively descriptions of ≥ 50 surprising and outstanding cases. In the table we summarize the most frequently mentioned somatic causes for fatigue ("the Big 5") as well as the rarest and most surprising diagnoses ("the Zebras").

"The Big 5" of Fatigue (number of cases)	"The Zebras" of Fatigue
1. Pharmacological causes (8)	Hypercalcemia in neurosarcoidosis
2. Morbus Addison (6)	Valium mistaken for vitamins
3. A) Hypothyroidism (5)	Porphyria
B) Infectious diseases (5)	Sheehan Syndrome
4. Cancer hidden by plausible alternatives (4)	Fatigue in Puberty ("nothing else")
5. A) Narcolepsy (3)	Acromegaly
B) Obstructive and central sleep apnea (3)	Nymphomania

[Table]
General take home messages:

- The rare reasons for fatigue and the near missed diagnoses by experts are valuable teaching tools.
- Generate new hypotheses if fatigue is explained by a disease, but does not improve during treatment.
- Be persistent - the devil is in the details.

Specific learning points:

- Make the distinction between sleepiness and fatigue.
- More often than generally anticipated, the sound of hooves is actually due to zebras.
- "Think medication": The wrong dosage, the wrong substance, substance abuse, the medication of the wrong patient. Educate your patients on pharmacotherapy.
- If all else fails, take the patient history repetitively

P364 Asian patients: remember the TOFI - avoid the FOFI

Judith Maria Schwaiger
Universitätsspital, Zürich, Switzerland

Background: We treat an increasing number of patients from Asia. Typically these patients have often early onset metabolic derangements in the glucose and lipid metabolism at apparently "normal weight", i.e. body mass index (BMI) < 25 kg/m^2.
Case: A 32 year old Sri Lankan man (70 kg, 170 cm, body mass index (BMI) 24.2 kg/m^2) consulted our outpatient clinic due to symptoms which were caused most likely by **gastroesophageal** reflux disease. Antacid therapy lead to a relief of the symptoms. To the surprise of the doctor and the patient, the laboratory revealed elevated liver transaminases (ALT 98 U/L) and fasting triacylglycerol plasma concentration (3.17 mmol/L). Plasma glucose and HbA1c were normal. An ultrasound examination revealed a fatty liver. Autoimmune hepatitis, hemochromatosis or viral hepatitis were excluded. The final diagnosis was **steatosis hepatis** in a normal weighted patient, DD alcohol induced fatty liver disease (the patient was working in a restaurant). The patient was instructed about the higher risk due to his ancestry. A motivational therapy lead to a successful lifestyle change back to traditional Asian lifestyle with resolution of the medical problems.

Tab.1. BMI cutoff points and risk category for Asians

BMI Category	**BMI (kg/m2)**	**Risk Category**
Normal	18.5 - 22.9	Increasing but "acceptable" risk
Overweight	23 - 27.49	Increased risk
Obese	>27.5	High risk

Discussion: This patient is a typical Asian patient with an extremely high metabolic and cardiovascular risk. These patients show a different body composition as compared to Caucasians: for any BMI they do show a higher fat mass and higher abdominal fat mass leading to cardiovascular and metabolic risk. Accordingly the WHO formulated different BMI cutoff values for Asians (Tab. 1). These pathophysiologically important differences in body composition request a much more aggressive therapy of metabolic risk factors (obesity, physical inactivity etc.) in Asians early in life. The application of the Asian cutoff points for overweight and obesity should be applied in all Asian patients since they are all TOFIs - "thin outside but fat inside". With time they all become FOFIs - "fat outside and fat inside" - the latter being a high risk setting. Despite a large body of evidence this knowledge is hardly implemented in daily practice. Barriers for a successful implementation of these guidelines will be critically discussed.

P365 Case report: spontaneous unilateral neck swelling after isometric exertion

Annika Jantze[1], Gustav Andreisek[2], Christlieb Haller[1]
[1]Klinik für Innere Medizin, [2]Institut für Diagnostische und Interventionelle Radiologie, Universitätsspital Zürich, Zürich, Switzerland

A 32-year-old right-handed woman presented with a spontaneous, painless swelling of the right supraclavicular fossa and neck. She denied fever, night sweats or weight loss. There were no recent travels outside of central Europe and no specific risk factors. Prior to this presentation she was in excellent health and physically active.
Body temperature and vital parameters were normal. Physical examination showed a palpable soft tissue swelling of the ride side of the neck with pronounced asymmetry of the supraclavicular fossae without tenderness or dysphagia; the thyroid gland was unremarkable. There was no evidence of inflammation nor local or systemic lymphadenopathy or hepatosplenomegaly.

Laboratory investigations including C-reactive protein as well as a full blood count, thyroid and hepatic function parameters and antibody tests for toxoplasmosis and Bartonella henselae - because of her occupation as a veterinarian - were all within normal limits. Imaging by duplex ultrasound and magnetic resonance imaging (MRI) with angiography of the neck documented pronounced soft tissue edema of the anterior neck and right supraclavicular fossa extending via the prepectoral and presternal regions into the upper mediastinum. There was no pleural effusion.
Upon detailed history the patient reported that one day prior to presentation she had been to a social beer drinking event where she competed with her friends to extend a 1 litre beer-stein with the outstretched arm for as long as possible; reportedly she maintained this heavy isometric exercise until exhaustion.
A high-resolution MRI demonstrated a longitudinal fluid-filled structure ending abruptly. This could be interpreted as a ruptured lymphatic vessel caused by the unusual muscular exercise as rarely reported in the literature. Within one week the swelling had completely resolved and the patient resumed her regular activities indicating an excellent prognosis without specific treatment. We propose that the swelling was caused by extravasated lymphatic fluid due to the heavy isometric muscular exertion.

P366 Severe vitamin B12 deficiency in a patient with strict vegetarian diet and pernicious anemia

Christin Schneider, Stefan Schmid
Klinik für Innere Medizin, Seespital Horgen, Horgen, Switzerland

Case: A 84 year old woman presented at our emergency room with somnolence, hypotension, tachypnea, dehydration and slight jaundice. The blood test revealed a severe hypoproliferative, macroovalocytic anemia with hemoglobin levels at 59 g/l, and thrombocytes at 69 x10^9/l. The patient`s vitamin B12 levels were below detection limits. LDH, Ferritin and bilirubin levels were increased in the context of ineffective erythropoiesis and peripheral breakdown of the red blood cells. Furthermore, high creatinine levels indicated acute renal failure, which was certainly caused prerenal by anemia, and was further aggravated by diarrhea which she had suffered from over the previous days. Nevertheless, stool samples did not show any bacterial growth.
The patient refused a blood transfusion for religious reasons. However, with intravenous rehydration and replacement of vitamin B12 (subcutaneous), folic acid, zinc, and iron, the hemoglobin continuously increased to a maximum of 74 g/l at discharge time.
The etiology for this severe vitamin B12 deficiency was attributed to parietal cell antibodies, causing chronic atrophic gastritis and a lack of intrinsic factor (IF). Note that the patient was following a strict vegetarian diet.
Discussion: Lack of IF is a common but mostly underdiagnosed cause of vitamin B12 deficiency particularly with elderly patients. Pernicious anemia can either occur following gastrectomy or due to autoimmunity. One can detect anti-IF antibodies (45-60%) and/or gastric parietal cell-antibodies (80-90%). The strict vegetarian diet followed by the patient could well have aggravated her vitamin B12 deficiency. Besides typical anemia symptoms, the most common clinical neurological manifestation of vitamin B12 deficiency is subacute degeneration of the dorsal and lateral spinal columns. The patient did not suffer from paresthesia or ataxia but complained about several neuropsychiatric problems including a feeling of weakness and impaired memory. Following the substitution, such abnormalities improved.
Conclusion: This case report underlines the importance of checking autoimmune causes in patients with severe vitamin B12 deficiency.

P367 Application of a multimorbidity interaction matrix to evaluate therapeutic conflicts: a case report

Klarissa Siebenhuener[1,2], Vanessa Virgini[1], Dimitri Gassmann[1], Gregor Herfs[1], Edouard Battegay[1,2], Claudine Meindl-Fridez[1]
[1]Division of Internal Medicine, University Hospital Zurich, [2]Center of Competence Multimorbidity, University of Zurich, Zurich, Switzerland

Introduction: Multimorbid patients are often a major challenge due to therapeutic conflicts because of multiple interfering conditions. The aim of this case report is to present a framework of a multimorbidity interaction matrix, weighing individual therapeutic needs and the disease interaction potential (therapeutic conflicts).
Methods: We report on a case with multiple interfering conditions with application of a newly developed multimorbidity interaction matrix.
Results: A 54 year old man with hypertrophic cardiomyopathy due to hypertension presented to our Outpatient Department in 2005. The patient had a medical history of early-stage diabetes type 2 (HbA1C 6.6%) and reported of occasional alcohol consumption. Seven years later, in 2012, the patient developed depression and chronic alcohol abuse. Also, he had fallen several times with subsequent subarachnoid hemorrhage and one episode of an epileptic seizure, in combination with a new diagnosis of atrial fibrillation. His CHA2DS-VASC2 Score was 2.
The multimorbidity interaction matrix was used at the two different time points. According to our decision making process based on the interaction matrix we decided that the combination of atrial fibrillation with an increased risk of stroke against the risk of falls and bleeding was of primary importance. Due to this interaction and after discussion with experts we decided that undergoing closure of the left atrial appendage would be the optimal therapeutic option in such a constellation.
Conclusion: Medical decision making processes can be facilitated by the application of the multimorbidity interaction matrices, in which the framework provides a structure to complex medical conditions.
There is a need for studies that visualize and weigh typical dilemmas and therapeutic conflicts in multimorbid patients, since applicable treatment strategies for multiple conditions are poorly addressed in clinical practice guidelines and, in any case, need to be specifically individualized.

Postertour 2

Allgemeine Innere Medizin 6

Médecine interne générale 6

P368 Etablierung eines ethischen, pragmatischen, strukturierten Unterstützungsmodells an einem tertiären Spital - Pilotphase

Markus Hofer, Marianne Keller, Martina Jäggi, Regula Schmid, Berthold Rasche, Nicole De Lorenzi, Markus Wittwer, Peter E. Ballmer, Projekt Neuausrichtung Ethik KSW Kantonsspital Winterthur, Winterthur, Switzerland

Einleitung: Die Projektgruppe „*Neuausrichtung Ethik am KSW*“ wurde durch die Spitalleitung im Februar 2014 beauftragt, ein ethisches Unterstützungsmodell zu evaluieren und zu implementieren. Die *SAMW* hat 2012 Richtlinien zu Verfahren in Ethikunterstützung erlassen. Ziel dieser Verfahren ist es, anhand einer strukturierten Vorgabe bei einem ethischen Dilemma mögliche Handlungsoptionen zu generieren und priorisieren und Hilfestellungen für deren Umsetzungen zu geben.
Methode: Evaluiert wurden drei in verschiedenen Spitälern etablierte Verfahren: *7 Schritte Dialog* (*7-SD*, Institut Dialog Ethik), *METAP* (Abteilung Klinische Ethik der Universität Basel) und *SENSOR* (Dr. Dr. Christof Arn, ethikprojekte.ch). Diese drei Verfahren sind anhand eines Literaturstudiums (MH) und einer Befragung eines Experten des jeweiligen Verfahren in der Projektgruppe diskutiert worden. Resultierend aus dieser Analyse wurde ein eigenes Unterstützungsmodell erarbeitet.
Ergebnisse: Die untersuchten Verfahren weisen grundlegende Ähnlichkeiten, aber auch Unterschiede auf (siehe Tabelle 1).

	7-SD	METAP	SENSOR
Moderiert	Ja	Ja	Ja
Strukturiert	Ja	Ja	Ja
Geeignet für	Komplexe Probleme	Alle Probleme	Alle Probleme
Teilnehmer	Entscheidungsträger	Mit dem Fall Befasste	Mit dem Fall Befasste
Verbindlichkeit Entscheid	Stark	Orientierend	Nicht definiert
Trennung Fakten/Werte	Stark	Schwach	Stark
Bezug Normative Ethik	Prinzipienethik	Theorien-Pluralismus	Kohärentismus
Bezug zum Principlism	Stark (Autonomie)	Indirekt (Über-, Ungleich- und Unterversorgung)	kein Bezug
Überprüfung der Handlung	Ja	Ja	Nein

[Tabelle1]

Hauptunterschiede bestehen bezüglich der Trennung von Fakten und Werten, dem Bezug zur normativen Ethik, dem *Principlism* von Beauchamp und Childress, der Priorisierung der Handlungsoption und der Umsetzung im Spitalalltag.
Schlussfolgerungen: Jedes der evaluierten Verfahren weist Stärken aber auch Schwächen auf. Ausgehend von diesem Vergleich wurde ein eigenes Verfahren, angepasst an die lokalen Verhältnisse, entwickelt (Ethisches, pragmatisches, strukturiertes Unterstützungsmodell, *EpsUM*). Bei *EpsUM* handelt es sich wie bei *METAP* um ein 4-stufiges Eskalationsmodell (1. Eigene Orientierung, 2. Orientierung mit einem Mitglied der Moderationsgruppe, 3. Falldiskussion im Betreuungsteam und schliesslich 4. Besprechung in der gesamten Moderatorengruppe). Die Aufarbeitung einer ethischen Fragestellung gliedert sich basierend auf *METAP* und *SENSOR* in sechs Teilschritte:
1.) Formulierung der ethischen Fragestellung,
2.) Strukturierte ethische Anamnese,
3.) Analyse und Priorisierung der relevanten Werte,
4.) Generierung und
5.) Priorisierung und Überprüfung der Handlungsoptionen und schliesslich
6.) Umsetzung des Entscheides.
Inwieweit sich dieses eigenentwickelte Verfahren *EpsUM* im Spitalalltag bewährt, muss in einem nächsten Schritt weiter analysiert werden.

P369 Combined insulin aspart and atenolol poisoning in suicidal attempt

Lucas Weber[1], Barbara Federspiel[1], Reto Mettler[2]
[1]Klinik für Medizin, [2]Institut für Anästhesiologie, Intensiv- und Rettungsmedizin, SeeSpital Horgen, Horgen, Switzerland

Introduction: Characteristic features of beta-blocker overdose are hypotension, bradycardia, decreased systemic vascular resistance (SVR) and cardiogenic shock. Insulin overdose can lead to hypoglycemia, electrolyte imbalance and coma. A review of literature revealed only few reports of massive overdoses of either insulin aspart or atenolol. No reports of combined insulin and beta-blockers overdose were found.
Case: A 22 year old paramedical woman with no known comorbidities presented in hypoglycemic coma with an initial plasma glucose of 1.4mmol/l. At admission heart rate was 60 beats per minute and blood pressure was 105/70mm Hg. To counteract hypoglycemia, 500ml 10% glucose solution was administered immediately. Within 30 minutes she regained consciousness and reported, that approximately 45 minutes before admission, she had injected 1200 IU Insulin aspart in her tight (30% normal, 70% Isophan) and had ingested cumulatively 10g of atenolol (100 tablets of 10 grams). The following 64 hours a total of 18350ml

10% glucose Infusion were administered to keep glucose level in a normal range. Occurring potassium deficiencies were compensated orally. During the course of her ICU stay blood pressure and heart rate remained stable. The patient recovered without sequelae. Laboratory testing subsequently revealed high serum levels of atenolol with a peak at 13,4mg/l (therapeutic range 0.2-0.5 mg/l). After four days she was transferred to a psychiatric hospital for her depression.
Conclusion: In any case presenting with hypoglycemia and coma, insulin overdose should be kept in differential diagnosis, especially in paramedic personnel. We have successfully treated a severe case of combined poisoning with atenolol and Insulin aspart, both in potentially fatal dosage. In former case reports high dose insulin therapy along with glucose supplementation has been described as an effective treatment for severe beta-blocker poisoning [1]. The uncomplicated course with absence of severe cardiodepressive symptoms in our patient may be due to the combined overdose with insulin and the early onset of treatment.
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P370 A patient taking azathioprine admitted for fever

Patrick Raphael Bader, Dominik Müntener, Karin Fattinger
Medizinische Klinik, Kantonsspital Schaffhausen, Schaffhausen, Switzerland

Introduction: Azathioprine (AZA) is often used in autoimmune disorders such as myasthenia gravis (MG). AZA is a prodrug metabolized to the active metabolite 6-mercaptopurine (6-MP) within blood cells. 6-MP in turn reduces competitively purine synthesis leading to reduced lymphocyte generation and thus reduces circulating immunoglobulins and interleukin-2. However, the immunosuppressant AZA can also lead to serious side effects.
Case report: A 68-year old man, diagnosed with MG one year ago, was referred to our hospital by his neurologist because of worsening of MG associated with fever, shivering, malaise and myalgia for three days. AZA had been started four weeks ago. The physical examination and the chest X-ray did not provide any clues for a current infection. Beside of a C-reactive protein (CRP) of 152 mg/l, the laboratory work-up was unremarkable. The patient was admitted to our medical ward for clinical monitoring of MG and AZA was paused. Two days later MG symptoms had improved and all other symptoms were gone. Also CRP had decreased to 55 mg/l. Thus, the febrile episode was interpreted as a common cold, the patient was discharged and AZA resumed. A few hours after taking the next dose of AZA, the patient returned to our emergency room, since all symptoms had reappeared accompanied by a new reddish maculopapular rash on forearms and a livid painful lesion on the calf. Due to this clear chronology, we now suspected a side effect and diagnosed a hypersensitivity syndrome to AZA. AZA was replaced by cyclosporine for immunosuppression. Shortly thereafter the patient was dismissed in good health.
Discussion: At the time of the initial referral, we had focused on an infectious origin of the febrile illness in our patient under immunosuppression. However, at the end the re-appearance of the symptoms shortly after re-exposure, the Sweet-syndrome-like rash and the erythema nodosum led us to the correct diagnosis. AZA-induced hypersensitivity syndrome typically presents with acute onset of fever, constitutional symptoms and a variety of cutaneous lesions and occurs within four weeks after starting AZA (Cyrus N et al., JAMA Dermatol. 2013;149:592-7).
Conclusion: In patients under immunosuppression presenting with fever a thoroughly workup for infectious diseases is crucial. Nevertheless we must keep in mind, that there are other reasons for fever in such patients especially in those treated with AZA, such as an AZA-induced hypersensitivity syndrome.

P371 Second to third degree burns in a patient by simultaneous use of cigarettes and oxygen therapy

Elke Schmidt[1], Nadine Rauch[2], Albert Studer[1], Markus Diethelm[1]
[1]Kantonsspital St. Gallen, St. Gallen, [2]Spital Grabs, Grabs, Switzerland

Introduction: Supplemental oxygen is one of the most widely used therapies for people admitted to the hospital. Both patients and physicians are mostly not aware of the highly dangerous combination of oxygen therapy and continuous smoking.
Case report: A 50-year-old man with multiple consumption of drugs, nicotine and alcohol abuse was hospitalized because of severe ischemic colitis and subsegmental pulmonary embolism. Because of his hypoxia he received permanent oxygen by nasal cannula tubing. Despite all warnings he continued smoking. One evening he lit up a cigarette in the patient`s room. As a result of deep inhalation an intense flame burned the right cheeks. He suffered from second to third degree burns of the right ear, the nasal conchae and neck as well as the left temporal region (overall 11% of total body surface area). At the intensive care unit laryngoscopy could not identify any laryngeal edema, neither did the following bronchoscopy. The patient remained hemodynamically and respiratory stable. The burn was managed conservatively. There was no need of surgical intervention. After two days the patient was discharged from intensive care unit.
Combustion of most materials requires the presence of fuel, a heat source and an oxidizing agent. The fuel can consist of flammable hairspray, perfume or clothing, but also of the patient's skin and hair due to the inherent flammability of human tissue. Heat sources may include a lit cigarette or a spark thereof as well as faulty electrical equipment. Although oxygen on its own is not considered flammable it serves as a necessary component for a combustion as a powerful oxidizer. In most cases the fire began when the spark of a cigarette ignited the plastic tubing delivering the oxygen to the patient. The oxygen rushing through the tubing served to accelerate the flames, leading to serious burns of the head and neck in many cases.
Discussion: Despite all warnings about potential dangers, risk of burns and fire if cigarettes are accidentally lit in front of the oxygen, a considerable number of patients will continue to smoke while on oxygen supply. However reports of deaths are rare. Because they are threatening their own lives and especially the lives of those around them we have to calculate the risks and benefits of oxygen therapy in unconvincible smokers. Nevertheless, under certain circumstances, it would be legally allowed to withdraw the patient's smoking facilities in these situations if required.

P372 Identification of chronic conditions in the ICPC-2 for the use in multimorbid patients in primary care in Switzerland

Jérémie Blaser, Anouk Déruaz Luyet, A Alexandra N'Goran, Lilli Herzig, the Swiss Academy of Family Medicine consortium
Institut Universitaire de Médecine Générale, Policlinique médicale uniersitaire, Lausanne, Switzerland

The burden of chronic diseases in primary care is high, especially in multimorbid patients. Several definitions for chronic conditions exist, as well as, several lists of chronic conditions for inclusion in studies. A single list was established using the International Classification of Primary Care - second edition (ICPC-2) (O'Halloran et al., 2004). This list contained 147 items relating to chronic conditions. But, no indication on the frequency of these conditions in practice in family medicine or their relevance in the context of multimorbidity are given. Within the frame of the Swiss Academy of Family Medicine consortium, we aimed at establishing a list of chronic conditions based on the ICPC-2 classification to be used for the inclusion of multimorbid patients in studies conducted in primary care in Switzerland. We conducted a nationwide survey of general practitioners using Delphi and RAND methods. We started with all the items of the ICPC-2 classification and proceeded to a step-by-step elimination of items deemed not relating to a chronic condition. We used experts from five different regions: Basel, Zürich, Bern, Vaud and Geneva and the survey was conducted in German and French. The survey consisted in four steps. First a focus group of five experts was conducted to remove from the ICPC-2 classification irrelevant items in the context of chronic conditions. Then a three-steps online survey of experts was conducted. For each step the experts had to score 1) the chronic aspect of each remaining items (step 2 and 3) and 2) the relevance of each items in the context of multimorbidity (step 4). Data were analysed using the RAND/UCLA appropriateness method for the establishment of the final list of items.
Reference:
O´Halloran J, Miller GC, Britt H: Defining chronic conditions for primary care with ICPC-2- *Family Practice* 2004, 21(4):381-386.

P373 A case of drug rash with eosinophilia and systemic symptoms without initial eosinophilia

Brice Touilloux, Marco Mancinetti, Daniel Hayoz
Médecine interne, Hôpital Fribourgeois, Fribourg, Switzerland

We present a 69-year-old white female admitted to our hospital for a pruritic rash with high fever, diarrhea and vomiting . She has been taking allopurinol for 25 days for a suscpicion of gout. The patient presented with a deterioration of general status. We initially found elevated liver enzymes with high C-reactive protein, without lymphocytosis or eosinophilia but with the presence of atypical lymphocytes on blood smear. The eosinophilia appeared finally 10 days after the onset of the erythrodermia. We performed leg skin biopsies showing both a deep and superficial perivascular dermatitis. We discontinued all medications and began topical and systemic corticotherapy. The rash and pruritus progressively disappeared in about a week.
This case is an example of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) without eosinophilia or lymphocytosis at initial presentation. DRESS is known as a severe life-threatening drug-related disease. The symptoms are a widespread erythema and fever with involment of internal organs (often the liver), beginning 4 to 21 days after the first dose of incriminating drug. Eosinophilia and lymphocytosis are also found. It is an infrequent disease but the diagnosis should be considered in patient with a unexplained rash and systemic symptoms following a new medication, especially allopurinol.
By presenting this case, we intend to emphasize the possibility of having a DRESS without all typical signs at admission.

P374 Factor XIII (13) deficiency: a rare cause of bleeding

Cyrill Valentin Rütsche[1], Brigitte Brand[2], Esther Bachli[1]
[1]Medical Clinic Uster, Uster Hospital, Uster, [2]Division of Hematology, University Hospital Zurich, Zurich, Switzerland

Introduction: We describe a 72-year old male patient with recurrent bilateral subdural hematoma after a mild traumatic brain injury treated with several surgical interventions. The only risk factor for bleeding was a mild thrombocytopenia (70000/ml) due to a lymphoma. After correction of the thrombocytopenia the bleeding reoccurred and a further workup revealed a factor XIII deficiency (f13def) with a factor XIII (f13) activity of 32% (n: 70%-100%). Further evaluation excluded an acquired inhibitor for f13. A tentative diagnosis of a hereditary heterozygous f13def was made.
Methods: We performed a literature research using Pubmed with the keywords “factor XIII deficiency”, “acquired” and “hereditary”. Further analysis of family members and sequencing of f13 genes were performed.
Results: f13 is a transglutaminase which is activated by thrombin and stabilises and crosslinks fibrin molecules therefore playing a crucial role for normal haemostasis.
Congenital f13def is a very rare condition with a prevalence of one in 2 million and an autosomal recessive inheritance pattern. In homozygotes umbilical cord bleeding following the days after birth often is the first manifestation. Heterozygotes generally do not suffer from severe bleeding manifestations but may be at risk for bleeding after trauma, during pregnancy or surgical procedures.
Acquired f13def results mostly from consumption through disseminated intravascular coagulation, major surgery or autoantibodies against f13. In Japan the incidence of acquired f13def is 24 cases per year in a population of 128 million.
If f13def is suspected, f13 activity is measured in a functional assay. Autoantibodies against f13 are detected by a mixture test with a 1:1 mixture of patient and control plasma. If the measured activity of the mixture is lower than the average value of the patient and the control plasma, the presence of autoantibodies is suspected. This was not case in our patient. Genetic evaluation showed none of the most common mutations known to cause f13def. Substitution of f13 normalised the plasma values of f13 with the expected half life.
Conclusion: f13def is a rare condition which can cause severe bleeding complications. One should consider f13def in cases of bleeding which are unexplained and measure f13 activity.

P375 Expected health and quality of life and observed deficits in patients with primary and secondary lymphedema of the lower extremity

Kai Huggenberger[1], Stephan Wagner[2], Susanne Lehmann[1], André Aeschlimann[3], Beatrice Ammann-Vesti[4], Felix Angst[1]
[1]Forschung, [2]Angiologie, [3]Rheumatologie, Rehaclinic Zurzach, Bad Zurzach, [4]Angiologie, Universitätsspital Zürich, Zürich, Switzerland

Introduction: The aim of this study was to determine health and quality of life of "lower limb lymphedema" (LLL) patients stratified by primary and secondary lymphedema and to compare it with normative data.
Methods: A cross-sectional study of patients after treatment at the department of angiology of a rehabilitation clinic was conducted. Health and quality of life were measured by the Short Form 36 (SF-36) and compared to German population norms, stratified by age, sex and comorbidity.
Results: Primary LLL (n=52, 75% female, mean age 47.1 years) reported health comparable to normative values, e.g. SF-36 physical functioning 80.4 (norm 84.1, p=0.512) and SF-36 vitality 62.7 (59.7, p=0.117) (mean scores, 100=best). Secondary LLL (n=60, 68% female, mean age 60.6 years, 72% cancer survivors) scored 68.1 (73.9, p=0.049) and 55.2 (56.2, p=0.800) on the corresponding scales. Mean SF-36 role physical was worse than expected (60.7 versus 70.3, p=0.006) as well as SF-36 role emotional (70.5 versus 83.4, p=0.004) in sencondary LLL. Function, vitality and both SF-36 role dimensions were higher in primary LLL than in secondary LLL, (mean SF-36 vitality 62.7 versus 55.2).
Conclusion: Overall health and quality of life was high and comparable to the general population norms in primary LLL. The same was true for most psycho-social scales in secondary LLL whereas functionally some deficits were present, especially in both role dimensions. Cancer as the most frequent cause for secondary LLL may affect health in these dimensions. Negative effects of LLL seem to be well compensated, especially in primary LLL.

Postertour 2

Allgemeine Innere Medizin 7
Kardiologie / Pneumologie / Gastroenterologie 1

Médecine interne générale 7
Cardiologie / Pneumologie / Gastroentérologie 1

P376 Adrenocortical adenoma in adrenal gland causes fever and increased inflammatory blood parameters

Teresa Maria Thieke[1], Reinhard Imoberdorf[1], Peter Ballmer[1], Felix Grieder[1,2]
[1]Department of Medicine, [2]Department of Surgery, Kantonsspital Winterthur, Winterthur, Switzerland

Case: An 84-years old male Caucasian presented with a three days history of fever (39°C), fatigue and increased inflammatory parameters (CRP 241 mg/L, WBC 17,2x10^9 g/ l, TC 493x10^9 g/l). The PET-CT scan showed a mass of 5,5 cm in the left adrenal gland. After excluding a pheochromocytoma (PCC) an endosonographic cannulation of the adrenal mass with a biopsy showed hemorrhagic amorphous precipitates. However, no pathological findings (blood cultures, sonography abdomen, x-ray thorax, echocardiography) could be detected. An anti-inflammatory therapy temporarily reduced the fever but after stopping that therapy the fever recurred immediately. Thereafter the patient underwent laparoscopic left adrenalectomy and the mass was removed. Histology revealed an adrenocortical adenoma with central hemorrhage and multifocal myelo-lipomatous metaplasia. After the operation laboratory signs of inflammation normalised and the fever rapidly disappeared.
Discussion: Adrenal masses are often incidental findings in radiologic diagnostic. Symptoms can be flank pain [1] or as in the present patient fever and increased parameters of inflammation.
If inflammatory parameters are negative, the diagnostic procedure should be complemented with a PET CT scan [3]. Thereafter, the surgical (laparoscopic) removal of an adrenal mass of 6 cm is mandatory [2].

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[3] Venkata S. et al. Adrenal collision tumors and their mimics: multimodality imaging findings. Cancer Imaging. 2013;13:602-10. DOI: 10.1102/1470-7330.2013.0053

P377 Primary care in Switzerland gains strength - an update, track and international comparison of health system evolution

Sima Djalali, Tatjana Meier, Susann Hasler, Thomas Rosemann, Ryan Tandjung
Institut für Hausarztmedizin, Universität Zürich, Zürich, Switzerland

Background: Little is known about the development of the primary care (PC) status over time in specific countries with a traditionally weak primary care sector such as Switzerland.
Objective: We aimed to assess the current strength of PC in the Swiss health care system and to compare it with published results of earlier PC assessments in Switzerland and other countries.
Methods: A survey of experts and stakeholders of the Swiss health care system was carried out between February and March 2014. We used a self-administered questionnaire based on a set of 15 indicators for the assessment of PC strength. Concordance between the indicators of a strong PC system and the real situation in Swiss PC was rated with 0−2 points (low−high concordance).
Results: The response rate was 62.5%. Participants assigned 13 of 30 possible points to Swiss PC. Low scores were assigned because of an inequitable local distribution of medical resources, relatively low earnings of PC practitioners compared to specialists, low priority of PC in medical education and training, lack of formal guidelines for information transfer between PC practitioners and specialists and disregard of clinical routine data in the context of medical service planning.
Conclusion: Since an earlier assessment in 1995, an improvement of 7 indicators could be stated. As a result, Switzerland previously classified as a country with a low PC strength was reclassified as country with intermediate PC strength compared to 14 other countries. Low scored characteristics represent possible targets of future health care reforms.

P378 Threatening refeeding syndrome during the course of chemotherapy induced diarrhoea

Li Do[1], Maya Rühlin[2], Peter E. Ballmer[1]
[1]Departement Medizin, [2]Ernährungsberatung, Kantonsspital Winterthur, Winterthur, Switzerland

Case: A 73 years old woman with a locally limited but advanced gastric carcinoma was previously fed with enteral nutrition via needle catheter jejunostomy. After receiving the second cycle of a neoadjuvant chemotherapy she presented to our emergency department because of intense diarrhoea, nausea and severe deterioration of her general condition.
Blood analysis showed a low potassium induced by diarrhoea. An intravenous therapy with potassium and fluid was started; various oral antidiarrheal and antiemetic agents were given. Due to the continuing symptoms and progressive catabolic situation enteral nutrition was switched to a parenteral regimen slowly administered combined with the appropriate supplements. After starting total parenteral nutrition severe hypophosphataemia, hypomagnesaemia, and protracted hypokalaemia emerged with hypotension as a clinical complication, indicating a threatening refeeding syndrome (RS). The treatment with additional intravenous potassium phosphate and magnesium sulphate resulted in a normalisation of the serum electrolytes and amelioration of the general condition of the patient. In the meantime the enteral nutritional feeding could be slowly re-established.
Discussion: RS is a common, but underestimated and potentially fatal combination of metabolic derangements that can occur upon resuming of any type of nutritional intervention especially in

malnourished patients, e.g. patients with cancer, addiction to alcohol and anorexia mentalis [1].
Our patient was on enteral nutrition therapy before receiving two cycles of chemotherapy. Cytostatic drugs have the commonly known side effect of severe irritation of the mucous membrane and may cause a dramatic decrease of the intestinal absorption and digestion by diarrhoea. Furthermore the cytostatic drugs might have aggravated a pre-existing electrolyte imbalance. Moreover, enteral nutrition may not have been absorbed and therefore when started parenteral nutrition regimen severe electrolyte abnormalities occurred, a precursor of RS. RS is characterised by a rapid fall in serum phosphate, potassium and magnesium, which then may cause severe oedema and even fatal organ failure. Monitoring of these electrolytes is, therefore, of paramount importance to detect RS.

Literature:

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P379 Concurrent transverse myelitis and Guillain-Barré syndrome associated with campylobacter jejuni infection in an adult patient

L Muheim, T Rudolph, CA Meier, P Locher
Department of Internal Medicine and Specialities (DIMS), Stadtspital Triemli, Zürich, Zürich, Switzerland

We report on a case of a previously healthy, 54-year old patient, who developed severe tetraplegia with extended cranial nerve involvement one week after presenting with Campylobacter jejuni-associated gastroenteritis. The clinical course was complicated by the need for mechanical ventilation and severe autonomic dysfunction with recurrent asystolia requiring a permanent pacemaker device. Findings were consistent with the diagnosis of Guillain Barré syndrome (GBS) with cranial nerve involvement. Subsequent imaging studies and clinical evaluation led to the diagnosis of concomitant cervical transverse myelitis (TM). Both were interpreted as pathological immunological response to the recent infectious disorder.
TM is commonly treated with steroids, but little is known whether patients with clear association to GBS or Campylobacter jejuni infection respectively, would benefit from such an approach. We refrained from using steroids in this case, since we considered our patient to be at high risk for infectious complications during the prolonged critical care hospitalization. Treatment with intravenous immunoglobulins (2 courses of 0.4 g/kg, each over 5 days) was started instead. However, the patient remained neurologically severely impaired, still remaining tetraplegic after four months, while showing significant improvement of cranial nerve function.
Conclusion: Campylobacter jejuni infection may be associated with GBS or rarely with transverse myelitis. We report on a case of both GBS and TM occurring simultaneously after Campylobacter infection. Little is known about the effectiveness and risks of steroids in such overlap-syndromes and hence a case-specific approach is needed, assessing the global risks and benefits of steroid therapy.

P380 Rate and prognosis of missed pulmonary embolism in the emergency department

Christoph Keil[1], Christian Nickel[1], Achim Escher[2], Caspar Peterson[1], Roland Bingisser[1]
[1]Notfallstation, [2]Radiologie, Universitätsspital Basel, Basel, Switzerland

Introduction: The aim of this study was to determine the rate and prognosis of missed pulmonary embolism (PE) in patients presenting to the emergency department (ED) of the University Hospital Basel. We analyzed all ED patients with excluded and proven PE between January 2011 and December 2013.
Methods: Radiology, pathology, and clinical data were screened for PE. Comparing these databases, we determined the rate of missed PE. A PE was defined as missed if detected 24h after the patient presented to the ED or if it was detected by another department after the patient was transferred from the ED. Patients aged 18 years of age and older, receiving an ECG or any form of thoracic imaging were included. The primary endpoint of this study was the rate of missed PE at the emergency department and its prognosis.Patients with suspected pulmonary embolism and confirmed PE at the ED were accounted as true positive, patients with no suspicion for PE and no PE in their electronic health record were counted as true negatives. Patients with suspected PE without evidence for PE in the electronic health record were counted as false positive . Patients without suspicion for PE but with a diagnosis of 24 hours after ED presentation

were counted as missed (false negative).
Results: We screened 144000 patients that were reffered to the ED of our institution. Out of these 137743 received either an ECG or any form of thoracic imaging. 136397 patients had no history of pulmonary embolism in their electronic medical file and were therefore counted for true negatives. Of the remaining 1346 patients, 956 were suspected to have PE but did not show any signs of PE and were accounted for false positives. 214 patients had confirmed PE and 57 missed PE. Median age of patients with confirmed PE was 65.4 years, in the missed PE group the median age was 75.4. The main symptoms in the confirmed PE group were dyspnea (61,2%) and chest pain (48,8%) whereas only 26,8% of the patients in the missed PE group suffered from dyspnea and only 9,28% from chest pain. Mortality rate was 1.4% in the confirmed PE group and 46.3% in the missed PE group.
Discussion: Our study showed a PE detection-rate of 1:4 in our ED. To further reduce the risk of PE underdiagnoses, it may be necessary to increase D-Dimer testing, the use of venous ultrasonography and even increase the frequency of CT scans. Pulmonary embolism should always be considered, especially in patients with nonspecific symptoms.

P381 Incidental findings in computed tomography pulmonary angiograms (CTPA) and consequences drawn by emergency physicians

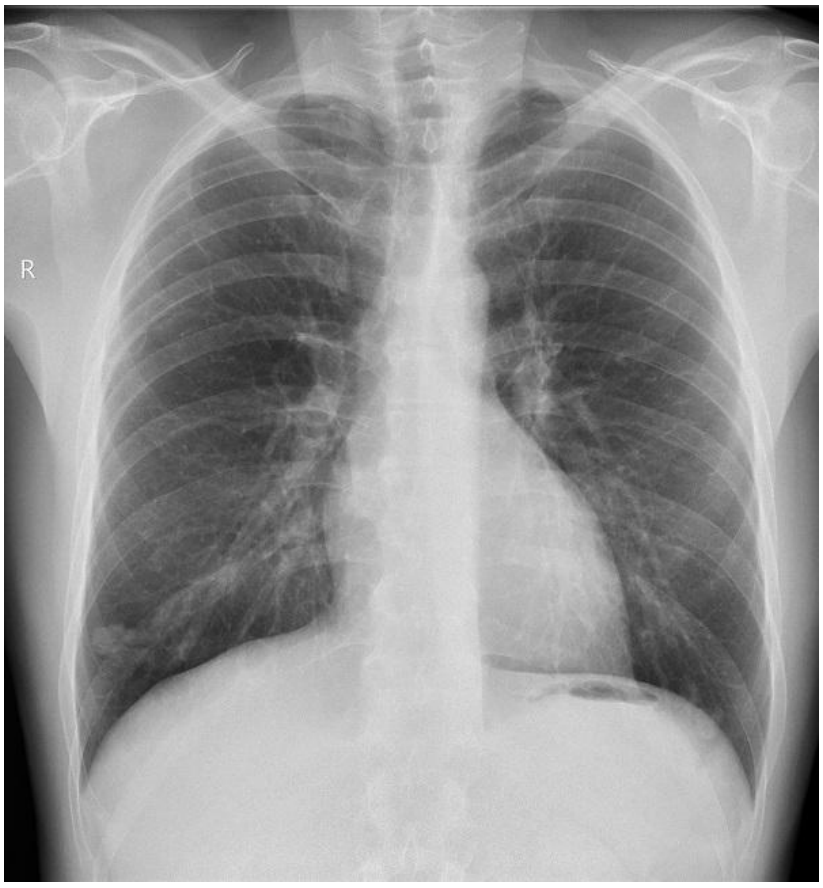
Christoph Keil[1], Alexandra Malinovska[1], Christian Nickel[1], Achim Escher[2], Tobias Käppeli[1], Roland Bingisser[1]
[1]Notfallstation, [2]Radiologie, Universitätsspital Basel, Basel, Switzerland

Introduction: CTPA is the standard method to diagnose pulmonary embolism (PE). After exclusion of PE, incidental findings (IF) are frequently reported, and may be missed by emergency physicians. We screened 956 CTPA reports from 2011 to 2013 for IF. It was our goal to determine the rate of these findings, the rate of subsequent diagnoses by emergency physicians based on these findings, and the rate of consequences drawn after incidental findings were described.
Methods: All CTPA reports of the Institute of Radiology of the University Hospital Basel ordered by emergency physicians between 2011 and 2013 were screened. Of 1346 CTPA, 214 PE were diagnosed, and 956 PE were excluded. A keyword search focusing on pathologies in patients with excluded PE was performed. An Expert panel defined 28 keywords. Chart abstraction was performed by two independent physicians. CTPA reports were compared to electronic patient records, and discharge reports. A framework was defined in order to assess if incidental findings were reported, if these findings were reported in the electronic patient record (e.g. as an individual diagnosis), and if these diagnoses were commented in discharge reports, and follow-up was recommended as suggested by radiology.
Results: In 536 out of 956 CTPA (56.1%) incidental findings were reported. In 435 of 536 patients (81.2%), these incidental findings were reported in the patient record. In 314 of 536 patients (58.6%) consequences were drawn by emergency physicians, usually by recommending follow-up examinations. The most frequent incidental findings were solitary pulmonary nodules (n=99, 13%), followed by pulmonary infiltrates (n=77, 9%), and intrapulmonary masses (n=34, 5%). Among extra-pulmonary incidental findings, suspected metastases (n=10, 2%) and rib fractures (n=9, 2%) were the most frequent incidental findings.
Discussion: Incidental findings in CTPA ordered for the exclusion of PE by emergency physicians were frequent. This is in line with previous findings. The important outcome in our cohort is the high rate of findings mentioned in electronic patient records. However, consequences were not always drawn, as only in 60% of all findings, a radiology-recommended follow-up was mentioned. We conclude that emergency physicians should be careful about incidental findings when discharging patients after exclusion of PE, and radiologists should be aware that emergency patients may be discharged before they report comprehensively.

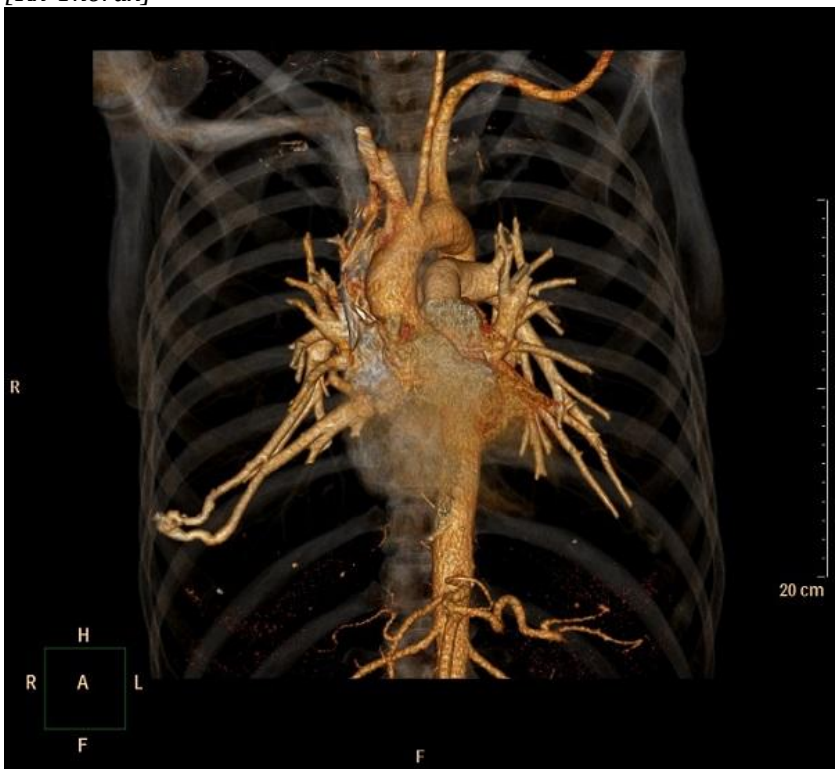
P382 Pulmonary arteriovenous malformations (PAVM): a rare cause of paradoxic embolization

Gianluca Hänny[1], Christina Jeanneret[1], Carmen Lienert[1], Ferdinand Martius[1], Andreas Häring[1], Helmut Rasch[2], Rolf Handschin[1]
[1]Innere Medizin, [2]Radiologie, Kantonsspital Baselland, Bruderholz, Switzerland

Background: Pulmonary arteriovenous malformations (PAVM) are abnormal communications between pulmonary veins and arteries. PAVM are rare. In 70-90% they are associated with hereditary hemorrhagic telangiectasia (HHT). Complications of PAVM are paradoxic embolization, brain abscess and pulmonary hemorrhage. Symptoms can be dyspnea, platypnea and headaches.
Case report: A 54-year old Patient presented to our hospital with recurrent episodes of paraesthesia of the left arm and speech disturbance. The Patient was known for a spleen infarction of unknown cause and suffered from migraine and recurrent epistaxis since adulthood. Suspecting cerebrovascular infarction, MRI-scan of the head was performed which showed two subacute infarct lesions in the right hemisphere, and also multiple older infarct lesions in the cerebellum. Holter-ECG was negative for atrial fibrillation. Duplex ultrasound showed mild atherosclerotic plaque on the right internal carotid artery. Because of cryptogenic stroke we perfomed a transesophageal contrast echocardiography which failed to show any embolic sources, including patent foramen ovale, but there was a significant non-cardiac right to left shunt shortly after the intravenous application of contrast bubbles (agitated saline mixed with blood). Chest x-ray and then pulmonary CT-scan was performed which revealed 3 pulmonary arteriovenous malformations. The diagnosis of paradoxic brain and spleen embolization caused by PAVM was established. The patient meets two out of four of the Curacao criteria for hereditary hemorrhagic telangiectasia (Epistaxis and PAVM) therefore rising a high suspicion for HHT. To investigate the importance of the right to left shunt-fraction through the lungs we performed a 100-percent oxygen test (performing an arterial blood gas analysis after inhaling 100-percent oxygen for 20 minutes through an airtight mask) which revealed a shunt-fraction of 18% (normal < =5%). The Patient is now discussed for pulmonary angiography and catheter-embolization of the PAVM´s to prevent further embolization. Genetic testing for HHT will also be performed.
Conclusion: A history of paradoxic embolization and a non-cardiac right to left shunt on transesophageal contrast echocardiography should raise the suspicion of PAVM. Pulmonary CT-scan can confirm the diagnosis. Symptomatic patients and patients with a feeding artery diameter of >= 2-3mm diameter should be discussed for catheter-embolization to prevent further complications.



[Rx-Thorax]



[Pulmonary-CT]

P383 Setting up a smoking cessation service - what can we expect from the first year?

Deborah Schneider[1], Andrea Meienberg[1], Anna Deman[1], Thilo Burkard[2]
[1]Klinik für Ambulante Innere Medizin, [2]Klinik für Ambulante Innere Medizin und Kardiologie, Universitätsspital Basel, Basel, Switzerland

Purpose: According to the WHO, smoking is the single most important preventable cause for premature death worldwide. Since different guidelines support to offer specialised tobacco treatment programs to smokers, we started a physician-led smoking cessation service (SCS) at a tertiary university hospital in 2012. SCS consultations on an individual basis were done by junior-physicians, supervised by senior physicians with special interest in smoking cessation. The present study presents our results of the first year of the SCS according to self-reported quit-rate and patient satisfaction.
Methods: In this cross-sectional study we included all patients (pts) consulting our SCS between 1.6.2012 - 31.5.2013. Baseline and treatment characteristics were obtained from pts charts. Pts were contacted by telephone or if not possible by letter for a standardized interview or questionnaire in February 2014 and self-reported smoking status and satisfaction with consultations (0=low, 10=high) were asked.
Results: 80 pts had their first SCS consultation during the first year. Follow-up (FU) data could be obtained from 68 pts, the remaining 12 were considered to be smokers. Mean FU was 430±95 days after their first SCS consultation. 41% of pts were male, mean age was 54±12 years, median Fagerström Dependency Level was 5 [4-7], 79% of pts had at least 1 smoking-associated comorbidity. Mean number of consultations was 2.9±2.3. 28.8% of all pts reported to be persistent abstinent (PA) over the past 7 days. Factors associated with PA were number of consultations and use of vareniclin. Comparing pts with ≤2 vs. >2 consultations PA rates were 20% vs. 40% (p=0.05). Median patient satisfaction was 8 [6-10], with 86.8% of pts stating that they would recommend the SCS to other smokers.
Conclusion: Our results show, that it is feasible to achieve persistent abstinence rates of 30% after a mean FU of 61 weeks and a high patient acceptance of the SCS - even in the first year. Our outcome in real-life pts is comparable to results of smoking cessation trials and could encourage further centers to set up a SCS.

Postertour 2

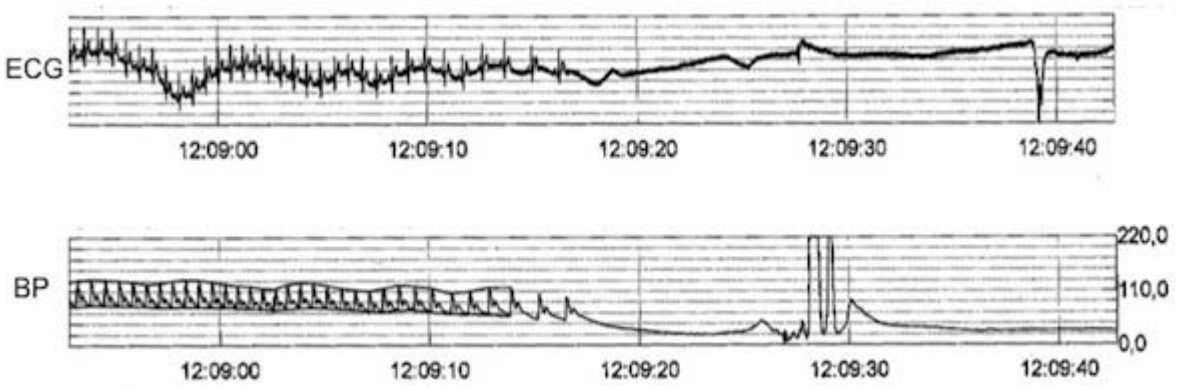
Kardiologie / Pneumologie / Gastroenterologie 2

Cardiologie / Pneumologie / Gastroentérologie 2

P384 Cognitive behavioral therapy for BIIP-type reflex syncope - a case report

Beat J. Meyer, Sebastian Slimack-Braun, Robert Küchler
Kardiologie Länggasse, HGZ Kardiologie AG, Bern, Switzerland

Introduction: Evidence for effective therapy of recurrent vasovagal syncope due to specific phobia is scarce. In severe cases, driving restrictions are common without effective therapy.
Case report: A 19 year-old freshly graduated commercial truck driver presented with a prolonged convulsive syncope during a hospital visit of his friend who had just undergone orthopedic surgery at the university hospital.
His past history revealed blood-injection-injury phobia (BIIP) since the age of 8; his father also suffers from the same condition. Syncope occurred 3 to 4 times a year with little warning but without injury. Prolonged syncope led to seizure-like symptoms but full recovery never lasted more than a couple minutes. Full cardiologic and neurologic work-up including physical examination with orthostatic challenge, ECG, Holter-monitoring, echocardiography, EEG, and MRI of the head showed no abnormality.
Finally, while preparing for a head-up tilt test an attempted venipuncture was associated with sinus bradycardia followed by asystole that was combined with brief tonic movements of arms and legs at 11 sec and lasted for a total of 40 sec (Figure).



[Asystolie von 40 Sekunden]
As a result the patient lost his commercial driver's license. Despite weak evidence he was offered a pacemaker therapy to reduce his syncope burden. [2,3] Instead, he chose a referral for psychiatric exposure therapy for his longstanding BIIP.
Psychiatric assessment prior to therapy using a validated questionnaire revealed a severe BIIP with a score of 106 out of 140 points. [4] Between September 2013 and March 2014 the patient attended 23 individual sessions of cognitive behavioral therapy (CBT) including coping strategies and increasing intensities of exposure to blood, injuries and injections. He no longer experienced prodromal symptoms or syncopes even during a regular blood donation. His final test score of 51 was below the cut off for the BIIP-diagnosis resulting in the reissue of his commercial driver's license.
Conclusion: This case describes a common form of recurrent reflex syncope with unusually long episodes of asystole for up to 40 seconds. Following successful cognitive behavioral therapy previously suggested pacemaker implantation turned out to be unnecessary. This strategy with cardiac pacing delayed until the proper mechanism is determined harbors the potential of a non-invasive cure and deserves further investigation.

P385 Primary hyperventilation in the emergency department: a first overview

Carmen Andrea Pfortmueller[1], Sandra Elisabeth Pauchard[2], Alexander Benedtik Leichtle[3], Georg Martin Fiedler[3], Aristomenis Konstantinos Exadaktylos[2], Gregor Lindner[4]
[1]Klinik für Allgemeine Anästhesie, Intensivmedizin und Schmerztherapie, Medizinische Universität Wien, Wien, Austria, [2]Emergency Department, University and University Hospital of Bern, [3]Center of Laboratory Medicine, University Institute of Clinical Chemistry, University Hospital and University of Bern, Bern, [4]Notfallzentrum, Klink am Park, Hirslanden AG, Zürich, Switzerland

Background: Hyperventilation is defined as a state of alveolar ventilation in excess of metabolic requirements, leading to decreased arterial partial pressure of carbon dioxide.
The primary aim of this study was to characterise patients diagnosed with primary hyperventilation in the ED.
Methods: Our retrospective cohort study comprised adult (≥16 years) patients admitted to our ED between 1 January 2006 and 31 December 2012 with the primary diagnosis of primary (=psychogenic) hyperventilation.
Results: A total of 616 patients were eligible for study. Participants were predominantely female (341 [55.4%] female versus 275 [44.6%] male respectively, $p < 0.0001$). The mean age was 36.5 years (SD 15.52, range 16-85). Patients in their twenties were the most common age group (181, 29.4%), followed by patients in their thirties (121, 21.6%). Most patients presented at out-of-office hours (331 [53.7%]. The most common symptom was fear (586, 95.1%), followed by paraesthesia (379, 61.5%) and dizziness (306, 49.7%). Almost a third (30.4%, 187) of our patients had previously experienced an episode of hyperventilation and half (50.5%, 311) of patients had a psychiatric co-morbidity.
Conclusion: Primary hyperventilation is a diagnostic chimera with a wide spectrum of symptoms. Patients of young age, female sex and with psychiatric comorbidity were more often diagnosed with hyperventilation syndrom without any further diagnostic evaluation.
In the future, further prospective multicentre studies are needed to evaluate and establish clear diagnostic criteria for hyperventilation and possible screening instruments.

P386 Patients and gastroenterologists' perceptions of treatments in Inflammatory Bowel Disease: do doctors and patients speak the same language?

Carla Vaucher[1], Michel H. Maillard[2], Marjan Timmer[1], Florian Froehlich[3], Bernard Burnand[1], Pierre Michetti[4], Valerie Pittet[1]
[1]Institute of Social & Preventive Medicine (IUMSP), [2]Service of Gastroenterology & Hepatology, Lausanne University Hospital, Lausanne, [3]Division of Gastroenterology & Hepatology, Basel University Hospital, Basel, [4]Crohn and Colitis Center, Clinique La Source-Beaulieu, Lausanne, Switzerland

Background: Perceptions of risks and benefits of therapies may differ between gastroenterologists (GIs) (as treatment providers) and inflammatory bowel disease (IBD) patients, (as treatment consumers). Few studies have focused on the patients' point of view on medication and prioritization of outcomes. The aim of this study was to explore and compare Swiss GIs' and patients' perceptions of appropriateness (i.e., balance of risks and benefits) of treatments for IBD.
Methods: Four vignette cases were drawn from typical clinical situations and formed the basis of three focus group discussions between either GIs (n=7), ulcerative colitis patients (UC-p, n=8) or Crohn's disease patients (CD-p, n=6). The contents of the three focus group discussions were compared using qualitative content analysis.
Results: UC-p agreed more often with GIs' treatment choices than CD-p. Most agreement was found around 5-ASA therapy, considered as the most convenient and safest drug to take. For CD-p, 5-ASA was often considered to be a placebo. For UC-p, topical 5-ASA was seen as a temporary solution, neither comfortable nor practical when professionally active; longer-term treatment with oral 5-ASA was preferred to azathioprine by both GIs and patients, who perceived azathioprine as the treatment for which the risks vs. benefits is the highest. Concerning anti-TNFs, the main risk perceived by patients was related to a potential loss of response. Divergences were observed on two main issues: 1) stop of treatment: UC-p did not easily

concur with stopping the treatments, which differed from the GIs' expectation of patients' perception; on the contrary, CD-p were more prone to consider stopping treatment than GIs; 2) perception of outcomes:

GIs aimed at obtaining a histological remission, and had a focus on long-term objective goals. In contrast, patients' expectations were of shorter term and focused on clinical remission, stress management, nutrition and information on treatments´ effects.
Conclusions: In the majority of cases, patients and GIs agreed on perceptions of treatments. However, GIs seemed more concerned about objective and scientific measures of remission whereas patients focused on quality of life and social outcomes when it came to evaluating a therapy. Better communication about those different goals & expectations may improve patients' adherence to therapy as well as physician-patient relationship, leading to better satisfaction with general healthcare.

P387 Case report of an 48-year old patient with a severe mycoplasma pneumonia infection

Eric Pascal Kuhn, Esther Bachli, Christian Alfaré
Internal Medicine, Hospital of Uster, Uster, Switzerland

Introduction: Mycoplasma pneumoniae is a common agent of upper and lower respiratory tract infections, mostly causing mild respiratory symptoms. We report a case with a severe clinical course, who presented in our hospital in Uster. The aim of this study was to investigate if there is an increase of positive reported Mycoplasma pneumonia infections in Zuerich.
Methods: We gathered the results of Mycoplasma pneumoniae PCR in respiratory secretions from different laboratories in Zuerich and compared them with those of prior years.
Results: We could detect an increase of positive Mycoplasma pneumoniae PCR reports, particularly in autumn of 2014.
Conclusions: Mycoplasma pneumoniae can cause critical infections. Rapid diagnosis and appropriate antibiotic therapy is necessary. Considering the observed increase of positive reports one should be aware of the possibility of such an infection.

P388 Asthma control and interest in participation in patient education seminars: data from the integrated care of asthma in Switzerland (INCAS)-study

Selina Dürr[1], Jonas Scheuzger[1,2], Kurt E. Hersberger[3], David Miedinger[1], Prashant N. Chhajed[1], Andreas Zeller[1], Claudia Steurer-Stey[4], Jörg Daniel Leuppi[1]
[1]University Clinic of Internal Medicine, Kantonsspital Baselland, Liestal, [2]University of Basel, [3]Department of Pharmaceutical Sciences, University of Basel, Basel, [4]Institute of General Practice, University of Zurich, Zurich, Switzerland

Introduction: Achievement of good asthma control is the goal of the Global Initiative for Asthma (GINA) guidelines. Patient education is one of the most important methods for achieving this.
Methods: Health insurance companies, pneumologists and pharmacists invited patients with asthma to complete a survey, which included the Asthma Control Test (ACT) and the Patients Assessment Chronic Illness Care Questionnaire (PACIC 5A). Patients were offered the possibility to take part in a patient education seminar run by the Swiss Lung Leagues or Swiss Allergy Centres (“aha”). The patients` overall asthma control, their satisfaction with the health care service they receive, and their interest in patient education were assessed.
Results: 223 asthma patients participated (mean age 43.2 ± 11.6 yrs; 38% males) in this study. Asthma was well-controlled in 145 (65%), not well-controlled in 45 (20%) and very poorly controlled in 32 (14%) patients (1 ACT score missing). 125 (56%) patients showed interest in taking part in an education seminar. Of these, 72 (58%) patients were well-controlled, 27 (22%) were not well-controlled and 25 (20%) were very poorly controlled. Mean PACIC and 5A summary scores were 2.05 ± 0.69 and 2.07 ± 0.75, respectively.

Conversely, of the 98 (44%) patients who were not interested in taking part in a seminar, 73 (75%) were well-controlled, 18 (18%) were not well-controlled and 7 (7%) very poorly controlled. Mean PACIC and 5A summary scores were 2.60 ± 0.87 and 2.74 ± 1.16.
Conclusions: Approximately one third of the patients showed uncontrolled asthma. In the group with interest in patient education, the portion of patients with uncontrolled asthma was much higher compared to the group without interest.

P389 An apple a day does not always keep the doctor away

Madleen Schmidt[1], Thomas Bregenzer[1], Jürg Knaus[2]
[1]Innere Medizin, [2]Chirurgie, Spital Lachen, Lachen, Switzerland

Introduction: Approximately 25 percent of patients with sigmoid diverticulosis will develop acute diverticulitis with complications. Diet fiber is supposed to modulate symptoms and decrease the risk of diverticulitis. However, wholesome nutrition may also constitute a risk for perforated diverticulitis.
Case report: An 87-year-old female patient was referred to our emergency room with a two week history of nausea, cramping postprandial abdominal pain and dizziness. On admission she was dehydrated with fever up to 39 °C and clinical peritonitis in the left and right lower abdomen. Signs and symptoms together with elevated inflammatory markers in laboratory findings yielded the clinical diagnosis of diverticulitis. Rehydration and intravenous antimicrobial therapy with ceftriaxone and metronidazole was initiated. A CT scan of the abdomen demonstrated a sigmoid perforation with free intraperitoneal air, a parasigmoidal abscess and a small foreign object as the cause of the illness. Open resection of the sigmoid colon was performed and intraoperative findings identified the perforating foreign body as an apple stem. The postoperative course was uneventful and the patient was discharged in good general condition eleven days after emergency admission.
Discussion and conclusion: In this unusual case report "healthy" nutrition with fruit did not prevent complications of diverticular disease but was rather the cause. Small unflexible pieces within the colonic stool bulk may be trapped in diverticulae and can lead to complications such as perforated diverticulitis. When patients with diverticular disease are counseled regarding dietary measures, advice should also be given to avoid potentially harmful bulking agents.

P390 How do patients adhere to chronic treatment of pulmonary diseases? Baseline data from an adherence study

Claudia Gregoriano[1,2], Simona Henny-Reinalter[1], Anja Hanschin[1], Anna Lisa Flamm[1], Thomas Dieterle[1], Isabelle Arnet[2], Kurt E. Hersberger[2], Jörg D. Leuppi[1,3]
[1]University Clinic of Internal Medicine, Kantonsspital Baselland, Liestal, [2]Pharmaceutical Care Research Group, University of Basel, [3]Medical Faculty, University of Basel, Basel, Switzerland

Introduction: Asthma and chronic obstructive pulmonary disease (COPD) are common lung diseases that require daily and mostly lifelong use of inhaled drugs. Despite important progress achieved in pharmacological and non-pharmacological treatment in recent years, control and management of symptoms remain suboptimal. As a consequence, recurrent exacerbations are likely to occur that may lead to reduced survival and deteriorated quality of life (QoL). Poor adherence to inhaled medication represents an avoidable risk factor. However, no data on adherence in Swiss COPD patients are available.
Methods: In this ongoing prospective single-blinded randomized controlled trial in- and outpatients with a diagnosis of asthma or COPD taking inhaled medication are recruited. Inclusion criteria are at least one exacerbation during the past 12 months. All participants get instructions about inhalation techniques with placebo devices. The intervention group is provided with an acoustic reminder for inhalation and receive support calls when use of rescue medication doubles.
Objective adherence are measured in both groups with electronic devices (Smartinhalers for puff inhalators and Polymedication Electronic Monitoring System for inhalation powder capsules) which record date and

time of each actuation. Medication adherence is calculated as inhaled puffs divided by prescribed puffs per day and displayed as percentage.
At baseline and at all visits, lung function measurements and questionnaires on adherence and QoL (St. George´s Respiratory Questionnaire, COPD assessment test SF-36) are performed.
Results: We present baseline date from the first 50 patients included in the study. The adherence is recorded during the first four weeks. The main results are shown in the following tables:

Patients characteristics	Age, Females	67.9 ± 8.5 years (Range: 34-82), n=13 (26%)
Diagnoses	COPD	n=41 (82 %)
	Asthma	n=7 (14 %)
	Asthma-COPD- Overlap	n=2 (4 %)
Medication	Short-acting Beta2- agonists (SABA)	n=28 (56 %)
	Long-acting Beta2 -agonists (LABA)	n=10 (20 %)
	Long- acting Anticholinergics	n=44 (88 %)
	Inhalaled corticosteroids (ICS)	n=2 (4 %)
	Combination of long-acting Anticholinergics plus Beta2-agonists	n=6 (12 %)
	Combination LABA plus ICS	n=36 (28.6 %)

[Baseline data]

Adherence	puff inhalers (metered dose inhaler, Turbohaler, Discus)	90.7 ± 21.0 % of prescribed dose (Range:46.0-160.0), n=35
	capsules containing inhalation powder	95.3 ± 7.8 % of prescribed dose (Range: 67.8-100.0), n=40
	Overall	93.3 ± 15.4 % of prescribed dose (Range:46.0-160), n=75

[Baseline Adherence]
Conclusion: In this ongoing study, the baseline adherence to inhaled medication is very high.

Postertour 3

Endokrinologie / Diabetik / Onkologie / Notfallmedizin 1

Endocrinologie / Diabétologie / Oncologie / Urgences 1

P391 Bilateral macronodular adrenal hyperplasia (BMAH) - a case report and new insights into pathophysiology

Martin Litzel, Zoran Erlic, Lea Slahor, Lukas Burget, Christoph Henzen, Stefan Fischli
Endokrinologie / Diabetologie, Luzerner Kantonsspital, Luzern, Switzerland

Case report: An abdominal MRI in a 43 year-old women showed incidentally discovered large bilateral adrenal masses. Personal history was uneventful with normal puberty and two unremarkable pregnancies. At that time she had no symtoms nor signs suggestive for hypercortisolism, hyperandrogenism or hyperaldosteronism.
Endocrine workup for hormone-activity showed normal levels of midnight salivary cortisol, aldosterone/renin and fractionated plasma-metanephrines. However 17-Hydroxyprogestrone (17-OHP) after admission of 250 µg Synacthen® was clearly elevated. Nine years later the women reported 20kg weight gain, light facial hair growth and new-onset arterial hypertension. Midnight salivary cortisol levels were repeatedly elevated but measurement of 24h urinary free cortisol was still normal.
Comment: Bilateral macronodular adrenal hyperplasia (BMAH) - formerly known as ACTH-independent macronodular adrenal hyperplasia (AIMAH) - is a rare cause of adrenal hypercortisolism and accounts for less than 2% of all Cushing´s syndrome (CS). Typically both adrenal glands are enlarged showing multiple nodules within the cortex. This entity is characterized by unique pathophysiological features:

1. Adrenal expression of ectopic aberrant hormone receptors (i.e. for LH, Vasopressin or gastric inhibitory peptide, [GIP]) that control cortisol secretion. This may lead to sporadic hypersecretion of cortisol (i.e. postprandial hypercortisolism through stimulation of GIP-receptors)
2. Control of cortisol secretion in a paracrine fashion by intranodular, direct production of ACTH.
3. A potential genetic background: In more than 50% of patients with BMAH germline mutations in the ARMC5-gene (armadillo repeat containing 5) can be found. Mutations were associated with more severe hypercortisolism.

Laboratory testing reveals often only subclinical CS that may progress over time. In the ACTH stimulation-test patients demonstrate high stimulated 17-OHP-levels due to ineffective cortisol synthesis but basal 17-OHP concentrations are normal (which is an important finding to differentiate between "classical" congenital adrenal hyperplasia [CAH] and BMAH). Usually, patients with severe Cushing´s syndrome are treated surgically by adrenalectomy.
Conclusion: BMAH is a rare cause of CS and diagnosis can be challenging. Recent studies revealed a paracrine mechanism of adrenal ACTH-dependent cortisol secretion and a genetic background.

P392 Ein Phäochromozytom mit wiederholt negativen freien Plasmametanephrinen

Anna-Lena Wolter, Philippe Rochat, Beat Frauchiger
Medizin, Kantonsspital Frauenfeld, Frauenfeld, Switzerland

Einleitung: Gemäß aktueller Evidenz gilt die Bestimmung der Metanephrine im Plasma in der Diagnostik des Phäochromozytoms als hochsensitiv, so dass im Allgemeinen davon ausgegangen wird, dass bei negativen Werten dieses ausgeschlossen werden kann. Der vorliegende Fall zeigt, dass die empfohlenen Laborparameter trotzdem im Stich lassen und den Weg zur Diagnose schwierig machen können.
Fall: Im Rahmen einer präoperativen CT- Untersuchung des Abdomens fiel bei einem 46- jährigen Patienten eine Raumforderung der rechten Nebenniere auf (30x19mm). Anamnestisch berichtete er über anfallsweise auftretende belastungsunabhängige einseitige Kopfschmerzen, thorakale Engen, Herzklopfen, Schwitzen und Schwindel seit ca. 3 Jahren. Zudem ungewollte Gewichtsabnahme von ca. 10kg. In der 24h-BD-Messung zeigte sich eine arterielle Hypertonie Grad I ohne nächtlichen BD- Abfall.

Die biochemischen Abklärungen waren bei wegweisender Anamnese und Bildgebung für ein Phäochromozytom nicht konklusiv. Lediglich Methoxytyramin im Plasma und die Ausscheidung von Normetanephrin und Noradrenalin im Urin lagen zunächst in einem grenzwertig erhöhten Bereich. In den Wiederholungsmessungen waren die freien Plasmametanephrine 4 mal normwertig, freies Normetanephrin in 2 von 4 Messungen grenzwertig erhöht, das freie Methoxytyramin in allen 4 Messungen erhöht (gemessen mittels LC-MS (Flüssigchromatografie mit Massenspektrometrie- Kopplung)).

Metanephrine (Plasma)	26.06.14	22.10.14	23.10.14	24.10.14	Einheit	Referenz
Metanephrin, frei	350	340	310	320	pmol/L	30-850
Normetanephrin, frei	1240	1470*	1570*	1260	pmol/L	40-1390
Methoxytyramine, frei	80*	120*	120*	130*	pmol/L	< 60

[Tabelle 1]

Katecholamine (24-h Urin)	08.07.14	23.10.14	Einheit	Referenz
Metanephrin	1321	1219	nmol/d	<1734
Metanephrin/Kreatinin	77	97	nmol/mmol	<180
Normetanephrin	4560*	4002*	nmol/d	<2420
Normetanephrin/Kreatinin	267*	319*	nmol/mmol	<250
Adrenalin/Kreatinin		6	nmol/K	<20
Noradrenalin		1037*	nmol/d	<570
Noradrenalin/Kreatinin		83*	nmol/K	<78
Dopamin/Kreatinin		149	nmol/K	<300
Kreatinin im 24h Urin	17.1	12.5	nmol/d	10.0-22.0

[Tabelle 2]

Da Anamnese und im Verlauf eine MRI- und F18-Dopa-PET-Untersuchung klar gegen ein triviales Adenom sprachen wurde die Indikation zur Adrenalektomie gestellt. Im histologischen Resektat bestätigte sich die Verdachtsdiagnose eines Phäochromozytoms. Der Patient gab postoperativ ein promptes Sistieren seiner Symptome an.
Diskussion: Bei wegweisender Klinik und Bildgebung waren bei diesem Patienten mit einem 3cm grossen, histologisch bestätigten Phäochromozytom die freien Metanephrine im Plasma wiederholt negativ. Aufgrund der in Folge nachgewiesenen Erhöhung des freien Methoxytyramins kann von einer Besonderheit des Katecholamin-Metabolismus im Tumor ausgegangen werden. Auch eine nur sehr periodische humorale Aktivität wäre denkbar.
Schlussfolgerung: Phäochromozytome können mittels der alleinigen Bestimmung der freien Plasmametanephrine verpasst werden. Je nach Literatur beträgt die Sensitivität der Plasmametanephrine 96 - 99%, die Spezifität 85 - 89%; für die Metanephrine und Katecholamine im 24-h-Urin je um 98%.

P393 Gynecomastia disclosing an estradiol-secreting testicular tumor - a case report

Lea Slahor, Stefan Fischli, Christoph Henzen
Endokrinologie und Diabetologie, Luzerner Kantonsspital, Luzern, Switzerland

Case report: An otherwise healthy 32-year-old man was referred to our out-patient clinics because of recent onset of bilateral breast enlargement. There was no loss of libido, no erectile dysfunction, no medication nor

co-morbidities reported. On physical examination body mass index was 27.8 kg/m2 and tender breast tissue was palpable bilaterally (4 cm in diameter). Testes were normal without palpable masses. Laboratory findings yielded a normal gonadal axis with total serum testosterone of 15 nmol/l (reference range: 5.7-28.1), sex hormone-binding globulin 56.3 nmol/l (reference range: 13.5-71.4), and LH 5.9 U/l (ref. range: 1.7-8.6). Prolactin levels were 9.7 ug/l (ref. range: 4-17). Serum tumor markers for testicular germ cell cancer such as alpha-fetoprotein, human chorionic gonadotropin and lactase dehydrogenase were negative. However, plasma estradiol concentration was markedly elevated at 304 pmol/l (ref. range: 28-156), corresponding to a low FSH of 0.9 U/l (ref. range: 1.6-11.0 U/l), and prompted further evaluation. A solid testicular mass was detected by scrotal sonography and histopathology after left semicastration revealed a 1.5 cm Leydig cell tumor (pTx N0 M0). Eventually, estradiol levels dropped to normal and gynecomastia regressed within 6 months.

Comment: Gynecomastia is caused by an androgen/estrogen imbalance like increased estrogen levels in men. Leydig cells are the main source of testicular androgens, but are also capable of estrogen production. Gynecomastia is present in 20 to 30 percent of patients with sex cord-stromal tumors of which Leydig cell tumor represent the most common subtype. On the other hand, germ cell tumors account for 95 percent of all testicular tumors, and their human chorionic gonadotropin secretion may also result in gynecomastia due to dyshormonogenesis and upregulation of aromatization within the Leydig cells.

Conclusion: We report a patient with a testicular Leydig cell tumor presenting with bilateral gynecomastia as the leading clinical symptom. Serum estradiol elevation led to diagnosis of this rare variant of testicular tumor. Our case report underlines the importance of estradiol measurement in new-onset gynecomastia.

P394 You reap what you sow! Case report of an immunocompromised patient treated with Depocyte®

Caroline Passaplan, Heiko Krause, Hans Ruedi Schmid, Jürg H Beer
Kantonsspital Baden, Baden, Switzerland

Introduction: We want to present the case of a 37-year-old male, immunocompromised patient diagnosed in April 2014 with an acute T-lymphoblastic leukemia. He was treated according to an established treatment protocol but presented complications on day +49: central nervous system symptoms like a doubtful meningism and bilateral facial paresis accompanied by strong pain.

Methods: Multiple clinical tests were performed to reveal the cause of the neurological symptoms. Among them a brain scan, magnetic resonance imaging and a head and neck exam which all came back negative. A treatment with intrathecal chemotherapy (Depocyte®) was started in combination with an irradiation of the CNS. Symptoms vanished, but struck by fate, 550 cells/µl were once again detected in the csf but the dignitiy and origin of these “cells” was far beyond conclusive. To be sure not to miss a differential diagnosis, we asked for the advice of a group of microbiologists and laboratory technicians by showing them images and a video of the the csf specimen.

Results: After tough brainstorming, we remembered, you reap what you sow: The patient was treated with i.t. Depocyte®, which is an injectable suspension of cytarabine encapsulated into Depofoam®. So we tried to reproduce these „cells“ invitro with a cell free csf of a healthy donor mixed with Depocyte®. We where able to identify the same strange appearing moving “cells” that we have found in the patients CSF sample by microscopic examination.

They again looked like parasites or blasts. So the differential diagnosis provided by the consulted microbiologists and laboratory technicians were mostly:

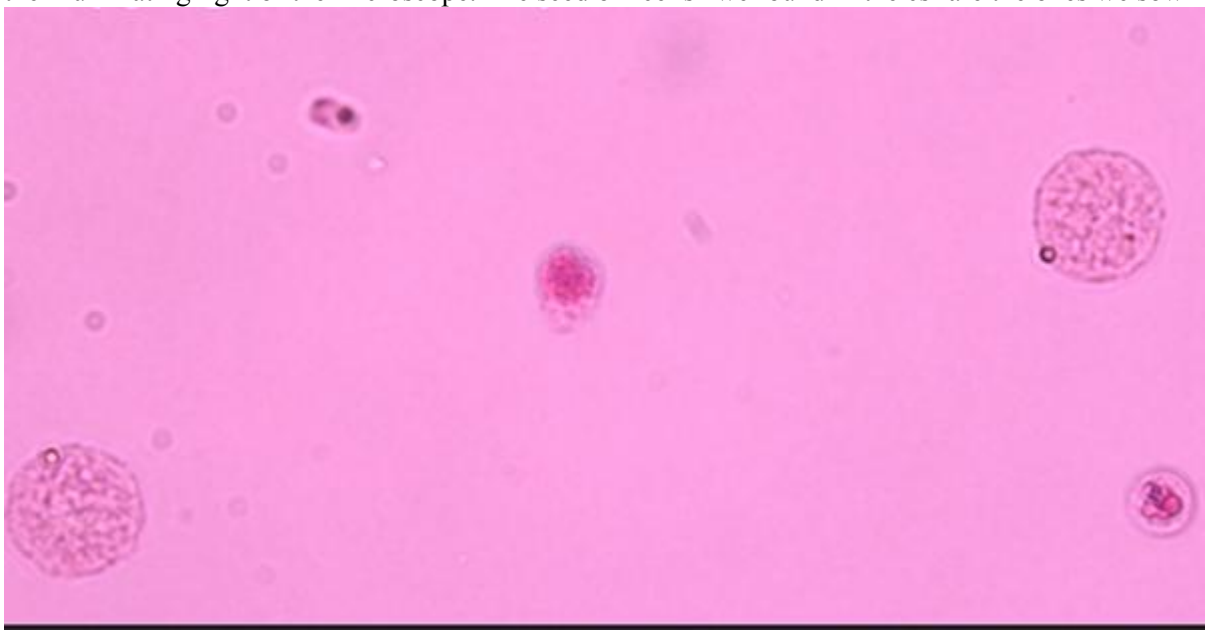
- Amoeba
- Naegleria
- Cyclospora species
- Leukemic blasts

So our weird moving “cells” looked definitely like parasites or even malignant cells.

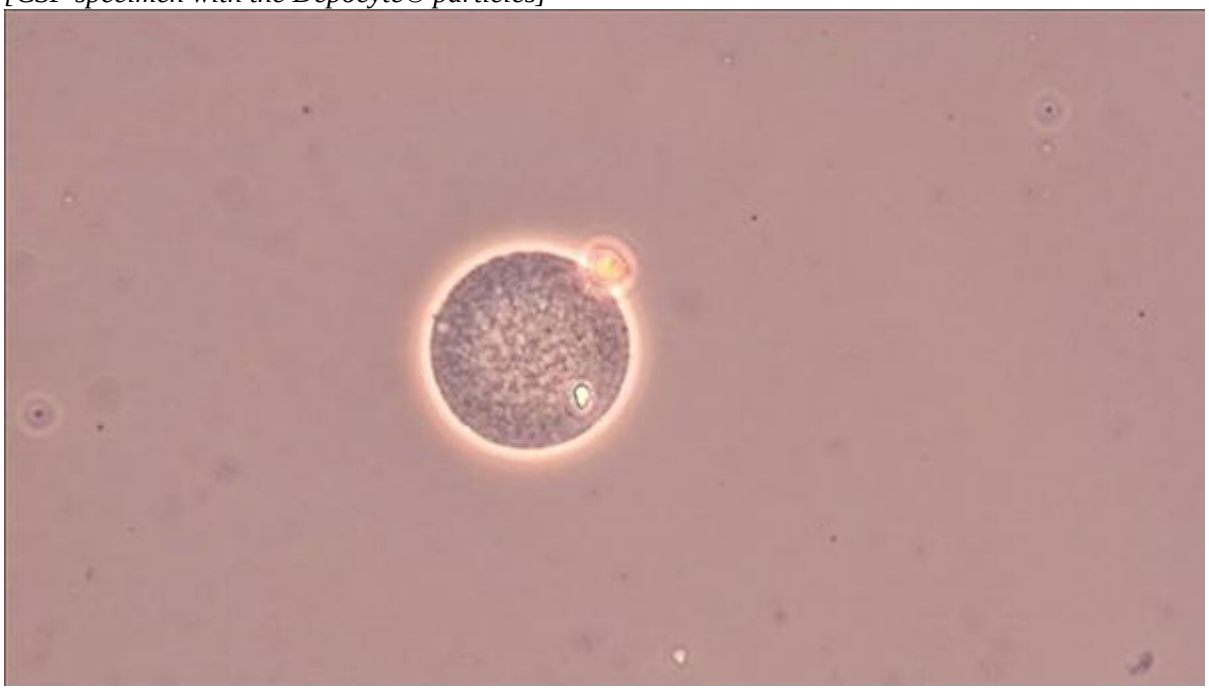
Conclusion: It's a trap, Depocyte® is not alive! Depocyte® lipid particles are morphologically quite similar to cells or parasites and can by seen up to 14 days in the csf. Virtually all consulted Microbiologists identified the Depocyte® particles as a species of parasites. Laboratory Technicians even misdiagnosed them as leukemic blasts.

Care must be taken after an i.t. injection of Depocyte®: the practician has to be aware that the “cells” seen

under the microscope are simply the lipid particles of Depocyte®, who are even moving due to the heat of the illuminating light of the microscope. The seed of "cells" we found in the csf are the ones we sow in prior!



[CSF specimen with the Depocyte® particles]



[Depocyte® particles phase contrast]

P395 Outcomes of electrical injuries in the emergency department: a 10-year retrospective study

Andrea Pawlik, Alina Lampart, Frank Stephan, Roland Bingisser, Wolfgang Ummenhofer, Christian Nickel
Universitätsspital Basel, Basel, Switzerland

Objective: Electrical injuries are challenging to assess and current guidelines are based on few studies and case reports. Recommendations regarding cardiac monitoring were published for certain risk factors, but

indications for hospital observation are less clear. Furthermore, the risk of late arrhythmias is not known. Therefore, we intended to assess possible cardiac complications, including death and immediate or delayed dysrhythmia after an electrical accident in a sample of patients presenting to the Emergency Department (ED).
Methods: Medical records of patients presenting to the ED of the University Hospital Basel, Switzerland, during 2004 - 2013 were retrospectively reviewed. Follow-up regarding the survival of these patients was achieved with hospital databases, direct contact with patients and caregivers. Primary endpoint was in hospital mortality and mortality within 10, 30 and 90 days, respectively. For our secondary endpoint, we investigated patient charts for occurrence of dysrhythmias and laboratory findings.
Results: During the study period, a total of 240 patients were identified. Twelve patients were lost to follow-up. Initial ECG was performed in 234 (97.5%) cases and 149 (62.1%) cases received cardiac monitoring. During the time of monitoring, 4 dysrhythmias (sinus bradycardia, 2 ventricular premature beats, and atrial fibrillation) were observed. All patients (n=238) survived, and no potential late serious dysrhythmia needing medical intervention was recorded.
Conclusion: No cardiac complications occurred during ED stay or during the 90-day follow-up period.

P396 Gemcitabin-induced TTP/HUS in a patient with pancreas carcinoma

Anna-Katharina Linneborn[1], Mirko Thiene[1], Daniele Siciliano[2], Bernd Yuen[3]
[1]Innere Medizin, Spital Bülach, [2]Onkologie, Onkologie-Praxis Bülach/Spital Bülach, [3]Intensivstation und Innere Medizin, Spital Bülach, Bülach, Switzerland

Background: The thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) in adults are defined by thrombocytopenia, microangiopathic hemolytic anemia, acute renal failure and neurological symptoms. There are different etiologies for these syndromes such as pathological activity of ADAMTS13 (vWF-cleavaging protease), drug side effects, malignancies and infections. Timely diagnosis is important because disease progression may be rapid with fatal outcomes in 10%. In cases of deficiency of ADAMTS13 plasma exchange would be the therapeutic gold standard. In cases of a drug side effect without ADAMTS13 deficiency treatment of choice would be supportive therapy.
Case presentation: In this case we report about a rare complication of gemcitabine induced TTP/HUS in a 58-year-old patient with pancreatic carcinoma. Before the diagnosis was made the patient received the second cycle of an adjuvant chemotherapy with gemcitabine. The patient presented to the emergency department with nonspecific deterioration of his general health condition, slight abdominal pain and undirected vertigo. Following the symptoms aggravated rapidly with dyspnea and further neurological symptoms (encephalopathy and hemiparesis). The laboratory examination showed an acute renal failure (creatinine 323 µmol) and a thrombocytopenia (44.00/ µl) with fragmentocytes in the differential blood count as a hint of hemolytic anaemia. Therafter the patient was treated with a hemofiltration, because a drug side effect-induced TTP/HUS was suggested.
Conclusion: This case is remarkable due to the fact that the complication of TTP/HUS occured already after a small cumulative dose of gemcitabine. It is important to think about the scarce complication of a TTP/HUS in patients with unclear neurological symptoms and acute renal failure, especially if they have a malignant disease or are treated with chemotherapeutic drugs.

P397 Impact on costs of a case management intervention for emergency department frequent users

Karine Moschetti[1,2], Katia Iglesias[3,4], Stéphanie Baggio[5], Venetia Velonaki[6], Ornella Ruggeri[7], Olivier Hugli[8], Bernard Burnand[9], Jean-Bernard Daeppen[10], Jean-Blaise Wasserfallen[11], Patrick Bodenmann[12]
[1]Institute of Social and Preventive Medicine (IUMSP), Healthcare Evaluation Unit, [2]Health Technology Assessment Unit, [3]Center for the Understanding of Social Processes, University of Neuchâtel, [4]Institute of Social and Preventive Medicine, [5]Life Course and Social Inequality Research Center, University of Lausanne, [6]Department of Community Medicine

and Public Health, Lausanne University Hospital, [7]Vulnerable Population Unit, Department of Ambulatory Care and Community Medicine, [8]Emergency Department, [9]Institute of Social and Preventive Medicine, [10]Alcohol Treatment Center, [11]Health Technology Assessment Unit, Lausanne University Hospital, [12]Department of Ambulatory Care and Community Medicine, Vulnerable Population Unit, Lausanne, Switzerland

Background: In most of the emergency departments (ED) in developed countries, a subset of patients visits the ED frequently. Despite their small numbers, these patients are the source of a disproportionally high number of all ED visits, and use a significant proportion of healthcare resources. They place a heavy economic burden on hospital and healthcare system budgets overall. In order to improve the management of these patients, the University hospital of Lausanne, Switzerland implemented a case management intervention (CM) between May 2012 and July 2013. In this randomized controlled trial, 250 frequent ED users (visits>5 during previous 12 months) were allocated to either the CM group or the standard ED care (SC) group and followed up for 12 months. The first result of the CM was to reduce significantly the ED visits. The present study examined whether the CM intervention also reduced the costs generated by the ED frequent users not only from the hospital perspective, but also from the healthcare system perspective.
Methods: Cost data were obtained from the hospital's analytical accounting system and from health insurances. Multivariate linear models including a fixed effect "group" and socio-demographic characteristics and health-related variables were run.
Results: Regressions showed that a higher age, Swiss citizenship, and having somatic health problems increased costs significantly. The coefficient associated with the CM group compared to SC group was negative (lower costs) from the hospital perspective, but positive in the analysis from the healthcare system perspective (higher costs). However, these two coefficients were not statistically significant.
Conclusions: The reduced costs from the hospital perspective of the CM group were likely a result of the success of the CM intervention in reducing the number of ED visits. The evaluation of costs from the health-care system perspective suggests that the CM intervention has also impacted the utilization of healthcare services by reorienting patients to medical and social services provided in the community. Further investigations into a larger sample, to increase the power of the analysis, and over a longer study period are required to validate to what extent the decrease in the number of emergency visits induced by case-management interventions translates into a reduction of the economic burden that ED frequent users place on hospital budgets, but also on health-care systems overall.

P398 Die Bedeutung von medizinischen Apps für die Gesundheitsversorgung von morgen

Andreas Trojan[1,2], Marco Egbring[2], Elmira Far[2], Gerd Kullak-Ublick[2]
[1]Onkologie, Brust-Zentrum Zürich, [2]Klinik für Klinische Pharmakologie und Toxikologie, Universitätsspital Zürich, Zürich, Switzerland

Die Nutzung von mobilen Applikationen (Apps) durch Ärzte und Patienten stellt uns nicht nur in der Forschung vor neue Aufgaben. Ethische und soziale Fragen müssen auf das neue Medium abgestimmt werden und die Arzt-Patienten- Beziehung in der engeren Kooperation mittels E-Health neu entdeckt werden. Eine grosse Herausforderung in der App-Entwicklung ist die stetige Anpassung an schnell fortschreitende technologische Entwicklungen. Eine App nach dem Prinzip „one app fits all" wird der komplexen medizinischen Thematik nicht gerecht und überfordert Patienten mit einer Informationsflut. Vielmehr benötigen Patienten speziell an den persönlichen Bedarf angepasste Apps, die vom behandelnden Arzt moderiert werden. Da Apps auch als Intervention fungieren können, sind Studien zur Validierung notwendig.
Wir haben hierfür eine randomisierte kontrollierte einfach blinde Studie zur zeitnahen Erfassung von Symptomen bei ambulanten Brustkrebspatientinnen initiiert (KEK-ZH-Nr. 2013-0200). Die Studie untersucht primär, ob die Nutzung einer, speziell für Brustkrebs-Patientinnen entwickelte, Smartphone-Applikation unter Einbezug des Arztes zu einem verbesserten Wohlbefinden und zu einer verbesserten Erfassung von Symptomen führt. Gleichzeitig ermitteln wir sekundär die Patientenzufriedenheit, Sicherheitsgefühl, die Strategien (Hilfsmittel) der Patientinnen für die Arztvisite, den Schweregrad der

Symptome, Notwendigkeit weiterer ärztlicher Hilfe, Anwendung von empfohlenen Pflegemassnahmen und Nutzungshäufigkeit der App. Die Patienten werden seit Dezember 2013 im Brust-Zentrum Zürich rekrutiert und auf freiwilliger Basis über drei Zyklen der Chemotherapie mittels Applikation begleitet.
Die Aufteilung von 150 randomisierten Patientinnen in 3 Gruppen ist wie folgt:
- Gruppe (A) erhält keine App und stellt die normale Patientenpopulation dar.
- Gruppe (B) erhält die App und erfasst strukturiert Wohlbefinden und Symptome im Verlauf, ohne dass der Arzt ("blind") über die Anwendung informiert wird. Hierbei wird untersucht, ob Anwendung der App die Patientenwahrnehmung verändert.
- Gruppe (C) erhält die App und erfasst wie die Gruppe (B) Wohlbefinden und Beschwerden. Diese Informationen werden zusammen mit dem Arzt während der Visite betrachtet und diskutiert.
Die Ergebnisse der Datenerfassung über die App und Fragebogen werden miteinander verglichen und die Unterschiede zwischen den Gruppen ermittelt.
Die Funktionsweise dieser App und erste Erfahrungen werden präsentiert.

Postertour 3

Onkologie/Notfallmedizin 2
Psychatrie/Neurologie

Oncologie/Urgences 2
Psychatrie/Neurologie

P399 Nothing but smoke?

Jana Grohmann[1], Jochen Beyer[2], Markus Diethelm[1]
[1]Klinik für Allgemeine Innere Medizin und Hausarztmedizin, [2]Institut für Rechtsmedizin, Kantonsspital St. Gallen, St. Gallen, Switzerland

Introduction: Cyanide (CN) is a mitochondrial toxin which is generated by the combustion of products containing carbon and nitrogen. These products are for example wool, silk and polyurethane. In case of intoxication by inhalation during a fire, CN can sometimes be considered to be the primary cause of death. Signs and symptoms appear within seconds to minutes after exposure.
Case report: We report on a 61-year old man who was rescued from a burning apartment in a state of unconsciousness (GCS 3). Primarily, his systolic blood pressure was 130 mmHg, the heart rate was 120 bpm and the respiratory rate was 6/min. After administration of 12 L of oxygen through a non-rebreathing face mask with a reservoir, the patient cleared up and was transported to our hospital. In the emergency room, the patient was hemodynamically stable and showed a GCS of 14. Abrasions on the back and soot particles in the nostrils were observed. The first arterial blood gas analysis (table 1) showed a carboxyhemoglobin of 36.2%, a metabolic acidosis with a lactate of 7.2 mmol/l. The other results were in the normal range except a hyperchromic macrocytic hemogram. In suspicion of a mixed intoxication with carbonmonoxide (CO) and CN, the patient was intubated and received a single dose of 5 g Cyanokit® (hydroxocobalamine). On the following day, the patient was extubated. All tested blood parameters had normalized and the patient could leave the hospital after 9 days. Blood collected at admssion was subsequently tested for the presence of toxic compounds. CN was detected at a concentration of 0.5 mg/l; additionally the blood showed a blood alcohol concentration of 0.22 %. The relation between CN concentration and severity of symptoms are as follows: concentrations in the range of 0.5-1 mg/l are considered as mild, between 1-2 mg/l as moderate, between 2-3 mg/l as severe with greater than 3 mg/l as potentially lethal. The results need to be interpreted with caution due to the short half-life of CN.

Parameter	Measured Values	Reference range
pH	7.241	(7.35 - 7.45)
pCO_2	5.42 kPa	(4.90 - 5.80)
pO_2	18.6 kPa	(10.0 - 12.0)
HCO_3^-	16.8 mmol/l	(21.0 - 28.0)
sO_2	98.2 %	(95.0 - 99.0)
FCOHb	36.2 %	(0.5 - 1.5)
Lac	7.2 mmol/l	(0.5 - 1.6)

[Arterial blood gas analysis]

Conclusion: The inhalation of smoke is the leading cause of death by fire. Even in cases of obvious CO intoxications, we should not forget the risk of additional CN intoxication during exposition to smoke in closed rooms. The high risk of CN intoxication and the negligible side effects of hydroxocobolamine justify an antidote treatment even in cases of suspected cyanide intoxication (table 2). Obviously, additional toxins - as in our case alcohol - should tested for.

Indication for hydroxcobalamine (Cyanokit®)
• exposition to smoke in closed rooms
• soot particles in the nostrils, the mouth and / or oropharynx
• impaired consciousness
When there exists in addition hypotonia and / or lactic acidosis (>10 mmol /l) there is a high-grade suspicion of a cyanide intoxication. This justifies the treatment with hydroxocobalamine.

[Indication for hydroxcobalamine]

P400 Emergency departments treatments of young people caused by violent acts

Mattia Lepori[1], Marilù Guigli[2], Ilaria Jermini-Gianinazzi[1], Rainero Spinelli[1], Davide Fadini[3], Emanuela Zamprogno[4], Antonia Lepori[5], Marco Galli[5]
[1]Ente Ospedaliero Cantonale, Bellinzona, [2]Ente Ospedaliero Cantonale, Locarno, [3]Ente Ospedaliero Cantonale, Mendrisio, [4]Ente Ospedaliero Cantonale, Lugano, [5]Dipartimento Socialita e Sanità, Bellinzona, Switzerland

Background: Youth violence is becoming a quantitative and qualitative significant phenomenon in Switzerland. Victims of violent acts are often young people, and the medical consequences of these events can be also serious.
Aim: The aim of the study is to evaluate from an epidemiological and clinical point of view, the incidence of youth violence phenomenon, in the Italian speaking part of Switzerland.
Methodology: We studied in a prospective way during a period of 4 months (June-September 2014) the characteristics of all patients younger than 25 years, who were treated in the Emergency Departments of public hospitals in Ticino.
Results: During the observed period 53 patients were treated by our medical services, because of a violent act. 7 patients were under the age of 16. Most of the aggressions (66%) took place out of the domestic space, and half of them happened in the nighttime (between 23:00 and 07:00). The aggressions were almost exclusively physical, and only 13% of them had sexual connotations. Most of the victims (77%) received outpatient treatments, while 23% of the patients had to stay in hospital (3 patients were also treated in an intensive care unit). The reported wounds were almost totally (85% of the events) of light or moderate seriousness; alcohol or drugs consumption was involved in 34 events (63%).
Conclusion: Young people's violence is a constant phenomenon, which also engages medical emergency departments. Fortunately, these episodes have almost always minor medical consequences, although a few serious events are observed. Alcohol or drugs abuse plays an important role in the origin of this issue.

Prevention and information campaigns are therefore necessary, in order to limit the extension of this phenomenon on our territory.

P401 Characteristics of the first 73 patients of the FUKNO (falls of unknown origin) study

Alexandra Malinovska, Christoph Keil, Christian H. Nickel, Roland Bingisser
Department of Emergency Medicine, University Hospital Basel, Basel, Switzerland

Introduction: Falls are a major problem in the fast growing elderly population. Previous studies showed that falls are either a surrogate marker for functional decline in the elderly or a sign for a new (or worsening) disease. Therefore, it is important to identify underlying causes for falls. Elderly patients presenting with falls to the Emergency department (ED) have a high risk for adverse outcomes, including higher morbidity and mortality and early admission to long term care.
The aim of the study is to identify the presenting complaints, the prevalence of underlying diseases, and the medical outcome in older patients presenting with falls. Furthermore, this study will be the basis for the establishment of risk stratification tools, and for disposition decisions. Primary outcome of this study is 30 day mortality; secondary outcomes are acute morbidity and institutionalisation.
Methods: The study is designed as a prospective multicentre observational study. Patients older than 65 years presenting to ED after falls and giving informed consent to participate, are enrolled in the study. At presentation, parameters such as demographic data, first overall clinical impression, activities of daily living, cognitive data, medical history, presenting complaints, vital signs, and standard laboratory examination are collected. Follow-up analysis is performed after 30 days and includes mortality, acute morbidity, and diagnoses responsible for admission. Data collection for 550 patients will be performed from 11/2014 until 09/2016.
Results: The characteristics of the first 73 enrolled patients collected were: 50 patients (68.5 %) were female, median age was 84 years. The average number of medication per patients was 4.5. Only 65.8% patients could recall their fall. Apart from the acute fall, the three most common presenting complaints were gait disturbance (57.7%), pain, unrelated to the fall (46.6%), and fatigue (34.3%). Currently we collect Follow-Up data for these patients. For the first 73 patients, in-hospital mortality was 0%.
Discussion: The major findings of this pilot study are the low mortality, in spite of the median age of 84 years, the presenting complaints (previously noted gait disturbance, chronic pain, and fatigue), and the fact that only two thirds even remembered the fall leading to emergency presentation.

P402 Vanishing liver metastases

Lukas T. Brylski, Marc Da Col, Peter E. Ballmer, Reinhard Imoberdorf
Department Medizin, Kantonsspital Winterthur, Winterthur, Switzerland

Introduction: Multiple myeloma (MM) is a common hematologic malignancy. It is characterized by proliferation of atypical plasma cells producing a monoclonal immunoglobulin. Proliferation usually takes place in the bone marrow. Extramedullary disease (EMD) in MM is a rare occurrence. With improved survival and increased imaging EMD is becoming more common. Nevertheless there are little data on the incidence of EMD and only sporadic case reports.
Case report: We report on a 70 year old patient in seriously reduced health condition with fatigue, bone pain and weight loss of more than 10% within four weeks. Abdominal ultrasound examination revealed hypoechogenic liver lesions highly suspicious for a metastatic disease. Further radiologic evaluation with contrast agent could not be performed because of acute renal failure (creatinine 523µmol/l, ref. 44-106µmol/l). Additional laboratory findings revealed a massive hypercalcemia (corr. serum calcium 3,2mmol/l, ref. 2.2-2.6mmol/l) and anemia (Hb 7,9g/dl, ref. 14,4-17,5g/dl). Lytic bone lesions were discovered on skeletal films. After further examinations and bone marrow aspiration, we diagnosed a multiple myeloma IgG kappa and started chemotherapy with Velcade, Cyclophosphamide, and Dexamethasone (VCD). After recovery of renal function we performed a MRI for follow-up of the liver

lesions that still were suspicious of a metastatic disease. We performed an ultrasound-guided biopsy few days later, but the supposed metastases nearly vanished in between. We were lucky to obtain a biopsy which revealed an extramedullary spread of MM.
Discussion: Hematogenous spread of MM, which is the underlying mechanism of EMD in the present case, can involve any tissue or organ. Most frequently skin, liver, kidney or the central nervous system are affected. The incidence of EMD is 7% to 18% at the time of diagnosis. Additional 6% of patients will develop EMD later in the course of the disease. The incidence of EMD is associated with a poor prognosis of MM. In the present patient we hypothesise that the liver lesions vanished as response to the chemotherapy of the MM.
Conclusion: Clinicians should be aware that MM can present as hypovascular lesions in the liver or other organs indistinguishable from metastatic disease. Further imaging may be useful and should be performed in patients in whom extramedullary involvement is suspected. A biopsy may be necessary for definitive diagnosis because of the morphologic similarity to metastatic disease.

P403 Abdominal aortic aneurysm rupture without blood loss: a rare case

Mark Patrick Schmiedeskamp, Bastian Jentsch, Ruedi Stieger, Daniel Höhener, Reinhard Imoberdorf
Kantonsspital Winterthur, Winterthur, Switzerland

Introduction: Aortocaval fistula is a rare complication of abdominal aortic aneurysms occurring in 1% of cases and accounting for 3 to 6% of all ruptured aortic aneurysms. Overall mortality of ruptured abdominal aortic aneurysms is 65%. Here we describe a fatal case of an aortocaval fistula despite immediate surgical intervention with typical clinical presentation.
Case: A 70-year old male patient was admitted after a collapse with acute thoracic pain radiating into both arms. An initial blood pressure of 90/37mmHg without arm-to-arm difference and heart rate of 80/min was measured by the paramedics. On admission he was hemodynamically stable, painless with a feeling of moderate thoracic pressure. Physical examination showed jugular venous distension and a pulsating abdominal mass with a loud systolic bruit that the patient had known for months but never seeked medical advice. The immediately performed CT scan confirmed the diagnosis of a large infrarenal abdominal aortic aneurysm of 9cm in diameter ruptured into the inferior vena cava producing an aortocaval fistula without retroperitoneal bleeding. In the process the patient deteriorated rapidly developing a pulseless electrical activity requiring repetitive cardiopulmonary resuscitation. Therefore an emergency laparotomy was performed immediately in the trauma room. Although the aorta could be cross-clamped rapidly with temporary stabilisation of circulation and the aortocaval fistula was oversawn, the patient developed pulseless electrical activity again and died.
Discussion: Our patient presented with typical symptoms and could be diagnosed rapidly. Despite immediate laparotomy and cross-clamping of the aorta he could not be stabilized. Besides the signs of acute right ventricular failure, autopsy revealed atheromatous pulmonary embolization most likely originating from the aneurysm wall. After all he had developed acute right ventricular failure due to a large arteriovenous shunt volume most likely reinforced by pulmonary embolism.

P404 Case report: palpable liver tumor as presenting complaint

Annika Jantze[1], Niklaus Schäfer[2], Christlieb Haller[1]
[1]Klinik für Innere Medizin, [2]Klinik für Nuklearmedizin, Universitätsspital Zürich, Zürich, Switzerland

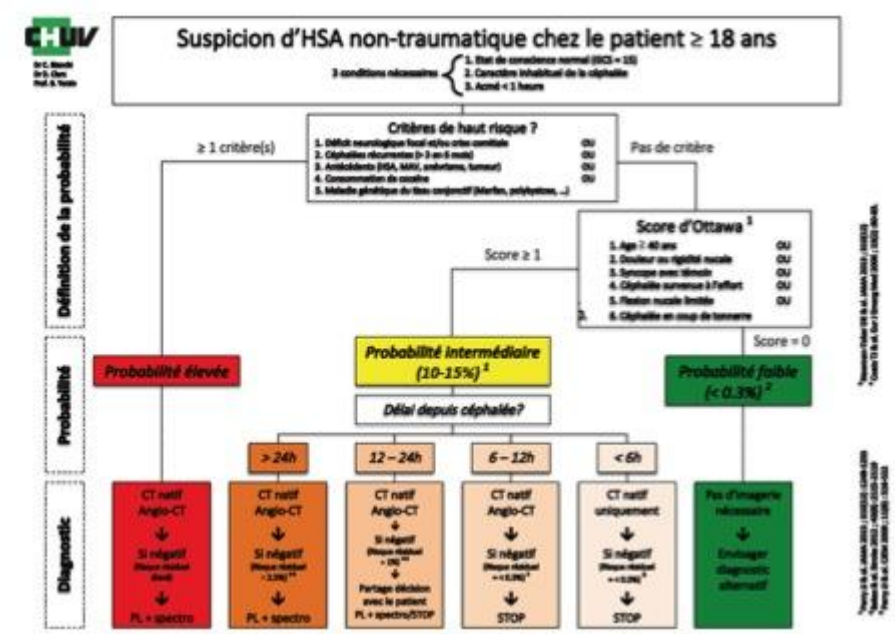
A 60-year-old man presented with a gigantic abdominal mass in the right upper quadrant which he had palpated himself. There were no other subjective complaints and he continued his daily activities with his usual energy. A detailed history was significant for an (intentional) weight loss of 20kg over 10 years with occasional loose stools, there was no diarrhea, vomiting or anorexia. He denied abdominal discomfort or

pain, travel to exotic locations, prior exposure to tuberculosis or B-symptoms. He was a smoker with occasional alcohol consumption. There was no fever, jaundice or cachexia. However, the liver was massively (even visibly) enlarged with a hard, painless central mass without physical signs of cirrhosis.
Thoraco-abdominal imaging by computerized tomography showed hepatomegaly and a large hepatic tumor with a necrotic core, multiple hypodense lesions scattered throughout the liver as well as bihilar lymphadenopathy and multiple osteosclerotic lesions. Laboratory investigations were remarkable for moderately elevated liver enzymes with non-diagnostic gastrointestinal tumor markers CA-19-9, AFP, CEA. In contrast, the concentration of chromogranin A in the blood was massively increased (10500 µg/l; normal range < 85 µg/l) suggesting a neuroendocrine tumor (NET). Biopsy of the liver mass confirmed the diagnosis of a NET expressing large amounts of synaptophysin on immunohistochemical analysis; the Mib1 index was 2% consistent with a NET grade G1-G2. Staging by somatostatin-receptor positron emission tomography (Ga-68DOTA-TATE-PET/CT) indicated an extensive spread of the tumor in liver, lymph nodes, bones and lung.
After discussion at the interdisciplinary neuroendocrine tumor board this patient with widely metastasized NET of unknown origin was offered primary systemic treatment with lanreotide (starting dose 60mg, subcutaneous injection) which was well tolerated and effective as evidenced by a rapid decline of the chromogranin A (6 weeks after the first dose 2844 µg/l).
Conclusions: The clinical and pathological presentation of NETs is extremely variable. Here we report a patient with a remarkable absence of symptoms despite extensively disseminated disease. This suggests a very slow growth of this particular (low grade) NET evidently not secreting biologically active substances. Individualized therapy was based on an interdisciplinary decision guided by clinical staging and pathological grading of this particular NET.

P405 Proposition d'un algorithme décisionnel clinique EBM pour la suspicion de l'hémorragie sous-arachnoïdienne non traumatique (HSA) aux urgences: revue de la littérature et analyse rétrospective locale des spectrophotométries positives

Christophe Bianchi, David Clerc, Bertrand Yersin
CHUV, Lausanne, Switzerland

Introduction: La PL fait partie du diagnostic d'une céphalée suspecte d'HSA anévrismale. L'objectif est de proposer un algorithme diagnostique rationnalisant l'utilisation de la PL et ne la réservant qu'aux patients à haut risque.
Méthode: Étude monocentrique et rétrospective dans un centre tertiaire, de 2005 à 2010, avec extraction de toutes les PL positives, ainsi que de tous les diagnostics finaux d'HSA, avec revue de dossiers.
Revue non-systématique de la littérature de 2009 à 2014, dans la base de données Pubmed, avec les termes « Aneurysmal Subarachnoid Hemorrhage » (MeSH Terms) AND « Diagnosis » (MeSH Terms).
Résultats: 869 PL extraites. 36 (4.1%) examens positifs, avec 14 (38.9%) dans un contexte d'HSA, et dont 3 HSA ont été diagnostiquées exclusivement par la PL (aucune d'origine anévrismale). Dans la même période, 235 HSA anévrismales diagnostiquées, dont 7 (2.9%) avec une imagerie cérébrale négative. Sur ces 7 cas, seuls 2 ont été diagnostiqués comme une HSA anévrismale (sensibilité CT-Scan 99.15%).
1904 articles identifiés, dont 98 inclus dans l'analyse.
Création d'un algorithme d'investigation d'une céphalée suspecte d'HSA, avec indications de recours à la PL selon la probabilité clinique et le délai depuis l'apparition des symptômes.



[Algorithme décisionnel EBM]

Discussion: Notre revue des PL permet de confirmer la faible spécificité de cet examen, même si elle reste limitée par son aspect rétrospectif et monocentrique.
Ces résultats, associés à la publication du score d'Ottawa, ainsi que l'amélioration continue de l'imagerie par CT et angio-CT, permettent de ne réserver la PL qu'aux patients à haut risque d'HSA anévrismale. La création de cet algorithme permet de rationnaliser l'utilisation de la PL et de ne réserver cet examen qu'aux patients à haut risque, malgré une imagerie négative.
La revue de littérature est limitée par le nombre restreint d'articles concernant le diagnostic de l'HSA.
Conclusions: La PL garde sa place dans le diagnostic de l'HSA, mais son utilisation peut être raisonnablement rationnalisée. En cas de suspicion d'HSA, l'excellente sensibilité d'un score clinique simple permet de mieux sélectionner les patients devant faire l'objet d'examens complémentaires. L'analyse spectrophotométrique du LCR garde certainement sa place dans cet algorithme d'investigation, notamment dans des contextes cliniques à haut risque ou lorsque la fenêtre diagnostique optimale du CT scanner est dépassée.

P406 Sexuality is a personal matter. The patient's needs to confess their sexual intimacy should not be overestimated

Vladimir Sibalic[1], Silke Henzen[2], Patrick Scheiwiler[3], Swiss Collegium for Research in Primary Care
[1]Arztpraxis, St. Gallen, [2]Arztpraxis, Sevelen, [3]Arztpraxis, Arnegg, Switzerland

Introduction: Literature in sexual medicine reports that approximately every third men and even more women suffer from sexual dysfunction. Health professionals claim that most people seek sexual healthcare. The results of an interrogative study in Switzerland suggest that 90.9% of male individuals want to talk with their physician about sexuality. However, other studies show that clinicians often avoid discussions about sexuality. Is it indispensable that primary care physicians take histories about sexual life routinely? Is there enough evidence of patients' need for such conversation?
Methods: 3 primary care physicians in eastern Switzerland questioned their patients in December 2014 during 2 consecutive weeks. Every patient in the waiting room (>18 years old) was asked to participate. No patients were excluded as long as they entered the doctor's office autonomously and self-determined even if they had a severe illness like cancer suffered from a psychological illness or were unable to understand the question which was written in German language. The question was explained to foreigners as required. The

participants answered the following single question anonymously and put the sheet of paper in a box: “Do you want to be interviewed by your family physician about your sexual life?” “YES” or “NO” If yes: a) today b) within 1 month c) within 3 months d) within 6 months.
Results: 143 patients (62.2%) did NOT want to talk about sexuality with their family physician. 400 patients were asked to participate. 230 patients participated (57.5% acceptance rate). Female gender: 54.8%. Among those who did want to be interviewed specified the answer as follows: today: 12(5.2%), within 1 month: 8(3.5%), within 3 months: 17(7.4%), within 6 months: 38(16.5%), missing answers: 12(5.2%)
Discussion: The restraint of primary care physicians to confront their permanent patients with questions about sexuality seems to be justified. The majority does not express a necessity to talk about their sexual life. Furthermore, most people who are not averse to talk about their intimacy do not urge. The results of this small patient survey contrast the results of the prior Swiss study. The patients' sexual risk behavior (number of sexual partners, concurrent partnership, symptoms of sexual transmitted disease, prior HIV tests) travel-medicine consultations and medical emergencies might differ in small primary-care office settings substantially from large outpatient clinics.

P407 Strong emotional stress as cause for a posterior reversible encephalopathy syndrome (PRES). A case report on “The Tako-Tsubo of the brain”

Ursina Manja Schmid[1], Frank Johannes Ahlhelm[2], Edlira Bekjiri[1], Petra Ferrari Pedrini[1], Annika Schade[3], Peter Stephan Sandor[3,4], Jürg Hans Beer[1,5], Andreas Rudolf Gantenbein[3]
[1]Department of Medicine, Cantonal Hospital of Baden, [2]Department of Radiology, Cantonal Hospital of Baden, [3]RehaClinic Bad Zurzach & Cantonal Hospital Baden, Baden, [4]University of Zurich, [5]Laboratory of Platelet Research, Molecular Cardiology, University of Zurich, Zurich, Switzerland

Background: Many different medical conditions may be associated with PRES. The syndrome is defined by typical clinical symptoms such as headache, visual changes, altered mental status and seizures as well as characteristic neuroradiological findings (mostly symmetrical white matter edema in the posterior cerebral hemisphere). As for the pathogenesis, both, failure of the autoregulation of cerebral perfusion and endothelial dysfunction are discussed.
Case description: A 51-year-old woman was submitted to the ER with a generalized tonic-clonic seizure five days after total thyroidectomy (struma multinodosa) with euthyreotic metabolic status. After having been informed about her mother's death, she was immediately suffering of strongest headache, dizziness and nausea. Two hours later, she had a first and shortly after, a second epileptic seizure. Blood pressure at arrival at the ER was 116/73 mmHg. There was no history of hypertension or any other vascular risk factor. Remarkably, during the thyroid surgery and the current hospitalization elevated blood pressure levels had been monitored. The cMRI showed bilateral occipital hyperintensities in the TIRM sequence, without diffusion restriction and with normal vascular status in the TOF-sequence, compatible with PRES. Extensive laboratory testings (e.g. for rheumatic and infectious diseases) showed no abnormalities besides the postoperative hypothyreosis.
A tapered seizure prophylaxis with clobazam over ten days was administered. Furthermore, an antihypertensive therapy with amlodipin and perindopril was initiated. In the follow-up after two months, the patient reported recurrent episodes of strong headaches in the initial phase, without any other neurological symptom. Cranial MRI was normal, with the posterior changes remitted.
Discussion: Similarly to a case report of PRES in a postpartum woman, we consider extreme emotional stress as a possible trigger of PRES. As some of the well-known comorbid medical conditions (e.g. eclampsia), emotional stress may cause PRES due to its secondary effects on blood pressure. In the above mentioned case report the MRI showed an edema due to local brain hypoxia. Our MRI findings are in line with vasogenic rather than cytotoxic brain edema, as a result of a disruption of the autoregulation of cerebral perfusion.
Conclusion: Our case supports the concept that extreme emotional stress may trigger PRES.

Postertour 3

Infektiologie / Immunologie / Rheumatologie 1

Infectiologie / Immunologie / Rhumatologie 1

P408 Rates and determinants of vaccination against seasonal and pandemic influenza in Swiss prehospital emergency medical services workers

Alexandre Moser[1], Cédric Mabire[2], Olivier Hugli[3], Victor Dorribo[4], Giorgio Zanetti[5], Catherine Lazor-Blanchet[6], Pierre-Nicolas Carron[7]
[1]Spital Zweisimmen, Zweisimmen, [2]University of Health Sciences (HESAV), [3]Service des urgences, Centre Hospitalier Universitaire Vaudois, [4]Institut universitaire romand de santé au travail, [5]Hospital Preventive Medicine Service, [6]Occupational Medicine, [7]Emergency Department, Lausanne University Hospital, Lausanne, Switzerland

Introduction: Influenza is a major concern for emergency medical services (EMS). EMS-Workers' (EMS-W) vaccination rates remain low. Determinants of vaccination for seasonal (SI) or pandemic influenza (PI) are unknown in this setting. We investigated influence of the H1N1 pandemic on EMS-W vaccination rates and determinants of influenza vaccination.
Methods: A multiple-choice questionnaire conducted in 2011, involving 65 EMS-W of the city of Lausanne, Switzerland. Demography, self-declared SI and PI vaccination status and motives for vaccine refusal or acceptation were collected.
Results: Response rate was 95.4% (n=62). 72.5% of EMS-W were young male, in good health; with more than 6 years of work experience in 74 %.Vaccination rates were 40.3% for both SI and PI, 19.3% for PI only, 1.6% for SI only, and 38.8% were not vaccinated at all. Women's vaccination rates (n= 17) were lower (23.5% for both SI and PI, 11.8% for PI only and 64.7% were not vaccinated at all). 92% of the EMS-W vaccinated against both PI and SI (PI+/SI+) received at least one SI vaccination during the previous 3 years (p=0.001). This rate was 8.3% in the PI-/SI- group (p = 0.001) and 25% in the PI+/SI- EMS-W (p=0.001). During the H1N1 pandemic, the SI vaccination rate increased from 25.8% during the preceding year to 41.9% (+62.4%)(p = 0.001). 30% of the PI+/SI+ EMS-W declared that they would not get vaccination during the following year. None of the PI-/SI- and PI+/SI- EMS-W was willing to be vaccinated in the future. Altruism and the discomfort induced by the mandatory mask wearing policy were the main motivations to get vaccination against PI. Factors limiting PI or SI vaccination included the option to wear a surgical mask, avoidance of drugs in general, fear of vaccine adverse effects and concerns about vaccine safety and efficiency.
Discussion: Average vaccination rate in our EMS-W was low, particularly in women, and not sufficient to prevent the spread of influenza. Previous vaccination status was a significant determinant of PI and future vaccinations. The mandatory surgical-mask wearing policy played a dual role, and its net impact on vaccination rate is probably limited. Our population was mixed and could be divided in 3 groups: favourable to all vaccinations, against all vaccination even in a pandemic context, and ambivalent towards vaccination with a “pandemic effect”. These results suggest a consistent vaccination pattern, only altered by exceptional circumstances.

P409 Persistent ACE-inhibitor-associated bradykininergic angioedema

Daniel Höhener[1], Anne Miller[1], Reinhard Imoberdorf[1], Marianne Lerch[2]
[1]Medizin, [2]Dermatologie, KSW, Winterthur, Switzerland

Case presentation: We report on a 60y old female patient admitted due to massive oedema of the face, the upper extremities, the upper part of the thorax and the ankles without urticaria or clinical signs of oral, respiratory or gastrointestinal involvement. Symptoms were progressive in the course of one week despite antihistamine and steroid therapy. The ACE-inhibitor medication which had been taken for several years, was discontinued three days after onset of the symptoms.

Diagnostic work-up: Based on the clinical picture of angioedema without urticaria histaminergic as well as bradykininergic angioedema had to be considered. After exclusion of internal causes like heart failure, superior vena cava syndrome, or nephrotic syndrome an extended complement analysis showed normal results for C1 esterase inhibitor concentration and function as well as C3c, C4, C1q. Further investigations showed no evidence for an underlying vasculitis, connective tissue disorder or systemic mastocytosis.
Clinical course: Because of progressive respiratory distress due to a thorax-wall oedema, a C1-inhibitor-concentrate (Berinert®) was given twice which resulted in a decrease of the symptoms within two weeks. However, due to a flare-up the application of icatibant, a direct inhibitor of the bradykinin receptor, was required leading to a prompt but not complete response. Therefore, a continuous treatment with tranexamic acid (Cyclokapron®) t.i.d. was installed resulting in a complete resolution after 10 weeks. Thus, tranexamic acid was tapered and eventually stopped 7 months after the initial presentation.
Discussion: The constellation of angioedema without urticaria non-reactive to treatment with antihistamines and steroids is suggestive of bradykininergic angioedema. As there was no evidence for hereditary angioedema, the prompt response to a C1 inhibitor preparation/bradykinin receptor antagonist points to an ACEI-associated mechanism though a combined mechanism cannot be excluded. Unlike in other cases of drug-induced angioedema, adverse reactions to ACEIs may develop long after the drug has been started. Acute treatment in bradykinin associated angioedema aims at increasing C1 inhibitor levels and/or directly reducing bradykinin effects/levels.

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P410 Rifampicin-resistant lymph node tuberculosis after inappropriate management of suspected latent tuberculosis

Anne Miller[1], Elisavet Moutzouri[1], Bettina Schulthess[2], Jaques Gubler[1], Urs Karrer[1]
[1]Department of Internal Medicine, Kantonsspital Winterthur, Winterthur, [2]Institute of Medical Microbiology, University Hospital Zürich, Zürich, Switzerland

Background: 70% of tuberculosis (TB) in Switzerland occurs among people originating from TB endemic areas (1). TB-exposed individuals are screened and treated for active or latent TB infection (LTBI). Swiss guidelines have recently been adapted to treat LTBI with Rifampicin (RIF) monotherapy for 4 months. We here report a case of RIF-resistant lymph node TB due to inadequate management of suspected LTBI after recent exposure to drug sensitive TB.
Case: In May 2014, a healthy 17-year-old immigrant from Somalia was diagnosed with LTBI based on a positive interferon gamma release assay and a normal chest-X-ray, both done after close contact with an index case suffering from drug sensitive, smear positive pulmonary TB. Monotherapy with RIF was initiated. Two months later, the patient developed fever, night sweats and weight loss followed by impressive supraclavicular lymph node swelling of 5x8cm. Needle biopsy revealed necrotising granulomatous inflammation and smear positive TB. Treatment with RIF, Isoniacid (INH), Pyrazinamid (PZA), Ethambutol (ETB), Moxifloxacin (MOX) and Amikacin (AMK) was initiated. After documentation of genotypic RIF-resistance but INH-susceptibility and occurrence of PZA-associated hepatitis, RIF and PZA were stopped and the patient was treated with AMK i.v., INH, ETB and MOX for additional 4 weeks, followed by INH, ETB and MOX without additional complications. He made a full clinical and laboratory recovery. This ongoing treatment regimen is planned for a minimal duration of 9 months.
Discussion: This patient most likely was already suffering from reactivated, drug sensitive lymph node TB when RIF-monotherapy for suspected LTBI was initiated, leading to RIF-resistance within 2 months. Since lymph node TB usually occurs years after primary TB, and exclusive RIF-resistance is very rare in Somalia (< 0.5%), new infection by recent exposure as well as reactivation of RIF-resistant TB is highly unlikely. Thus, this case illustrates that besides a chest X-ray, screening for active TB should at least include a

thorough physical examination and a urine analysis before monotherapy for LTBI is initiated, particularly in persons originating from areas of high TB endemicity. In addition, widespread use of RIF-monotherapy in LTBI according to questionable guidelines will inevitably lead to an increasing prevalence of RIF-resistance and subsequently to multi-drug-resistant TB.

References:

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P411 Otosyphilis: an uncommon manifestation of early neurosyphilis

Rupprecht Lange[1], Karolos Fostiropoulos[2], Jonas Rutishauser[1], Philip Tarr[1,3]
[1]University Clinic of Internal Medicine, Kantonsspital Baselland, [2]Clinic of ENT, Kantonsspital Baselland, [3]Infectious Diseases Service, Kantonsspital Baselland, Bruderholz, Switzerland

Introduction: In the last years a significant increase of syphilis cases, especially among men who have sex with men, has been reported in Switzerland (1). Central nervous system involvement can occur in patients with primary and secondary syphilis (2). Here we present a patient with facial palsy in the setting of unrecognized syphilis seroconversion that was followed 2 weeks later by typical secondary syphilis and sudden hearing loss.

Patient, methods and outcome: A 74-year-old male was hospitalized because of left sided facial palsy and visual disturbances of the left eye. MRI of the brain showed swelling of the left distal meatal branch of the facial nerve. Lumbar puncture results were normal including syphilis serology. The patient was treated with systemic glucocorticoids. 3 weeks later the patient presented with a sudden left sided hearing loss and a generalized maculopapular rash including the palms and soles. TPPA (1:10240) and VDRL titers (1:16) were positive, and HIV serology was negative. Repeat lumbar puncture showed normal results including negative cerebrospinal fluid syphilis serology. Secondary syphilis with involvement of cranial nerves VII und VIII was diagnosed.

Treatment with intravenous penicillin was given according to current Swiss recommendations (3, 4). 6 months later, VDRL titer showed an adequate (at least 4-fold) decrease (3).

Conclusion: Neurosyphilis is not restricted to late syphilis stages. Primary and secondary syphilis can in 25-60 % be accompanied by spirochetal invasion of the central nervous system which in approximately 5% is clinically symptomatic, typically presenting as cranial nerve palsies. Cerebrospinal fluid examination is negative in most cases of syphilis with inner ear involvement (5).

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P412 Late-onset hemolysis following the treatment of severe malaria with artesunate: a case report

Michela Cipriani[1], Helen Kovari[2], Sarah Elisabeth Braunias[1], Burbuque Ibrahimi[1], Dörthe Schmidt[1]
[1]Innere Medizin, [2]Infektiologie, Universitätsspital Zürich, Zürich, Switzerland

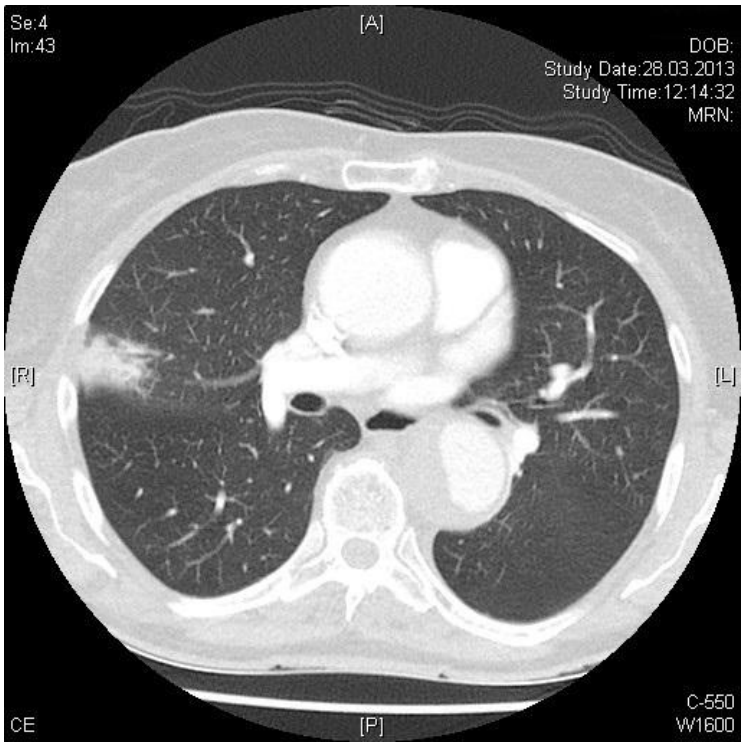
Objectives: Severe malaria is related to high mortality if not treated, and is generally defined as acute malaria with high levels of parasitemia (>5 percent) and/or major signs of organ dysfunction. The treatment

with parenteral artesunate is considered as first line therapy for severe malaria due to its superior parasite clearance and reduction in mortality compared to quinine. However, there have been an increasing number of reports of acute hemolysis following the application of artemisinin derivatives.
Methods: Herewith, we report a case of late-onset hemolysis after intravenous treatment with artesunate in a 47-year old male Russian patient, resident in Ivory Coast, with malaria tropica.
Results: No co-morbidities or prior medication, including lack of malaria prophylaxis, were present when the patient initially developed high fever and chills. Repatriating to Switzerland, poor clinical condition necessitated a direct transfer to an emergency ward at a German hospital. Severe malaria with acute kidney failure and an initial *P. falciparum*-parasitemia of 8 percent was diagnosed. The patient was treated with intravenous artesunate for three days, followed by piperaquine tetraphosphate/dihydroartemisinin perorally for another three days. After treatment, no malaria parasites were detected and the patient was discharged and journeyed on to Switzerland. Nine days after starting malaria-therapy the patient developed fever, chills and dark urine again. He presented therefore at our emergency ward. Blood analysis revealed hemolysis with increased lactate dehydrogenase (LDH) and elevated bilirubin, anemia with a hemoglobin drop of 5.5g/dl and high numbers of reticulocytes. Neither malaria parasites nor other causes for hemolysis were identified. Thus, late artesunate-related hemolysis due to recirculation of "pitted" and consequently delayed lysing erythrocytes was most likely. Transfusion of a total of 7 units of red blood cells was administered over 7 days. On day 13, LDH peaked by 5000 U/L, and haemoglobin concentration levels stabilized. The clinical condition of the patient improved.
Conclusions: Late artesunate-related hemolysis is a possible, rare side effect of malaria treatment. Further long-term safety and follow-up studies are required to better understand the underlying pathology and to identify the patients most at risk.

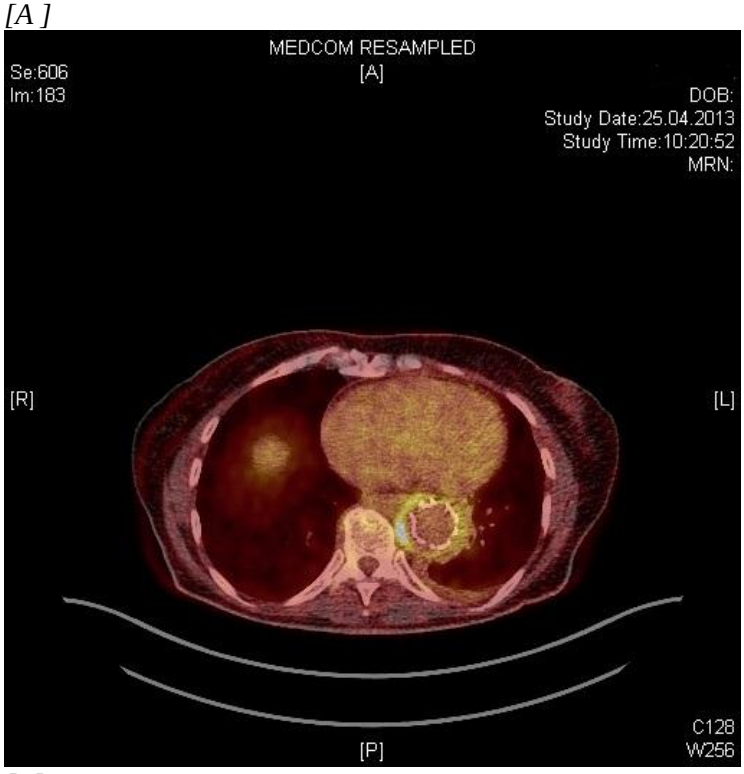
P413 The long query for the right diagnosis

Emanuel Bührer, Armin Stucki, Thomas Stöckli
Medizinische Klinik, Bürgerspital Solothurn, Solothurn, Switzerland

Case report: A previously healthy 69-year-old women was seen by her family physician for chest pain and fever. In a chest X-ray, pneumonia of the right lung was diagnosed. Antibiotic treatment with Amoxicillin/Clavulanic acid was started. For lack of improvement over the following two weeks, a thoracic CT scan was asked for. It showed a right upper lobe pulmonary infiltrate and a long aneurysm of the descending aortic artery, without dissection (A). The patient was urgently transferred to a center for thoracic surgery. A stentgraft was implanted into the descending thoracic aorta. Postoperatively, the patient was transferred to a medical ward of our hospital. She had persistent fever, night sweats and chest pain. At the time of her admission, inflammation markers were elevated: C-reactive protein 176 mg/l, procalcitonin 0.2 ng/ml, and leucocytes 8.9 x10^9/l. Two sets of blood cultures were negative. Serology for Treponema pallidum was also negative. A transthoracic echocardiography showed no signs of endocarditis. A PET-CT with F-18 FDG revealed increased activity within the aneurysm (B). Finally, serology for Coxiella burnetti was obtained. Phase I IgG were 1280 and phase II IgG 20480, consistent with chronic infection. Treatment with doxycycline 100mg 1-0-1 was begun, leading to rapid clinical improvement and decline of inflammation markers.
Comment: Q fever is caused by Coxiella burnetti, a gram-negative intracellular bacterium. It is a zoonotic pathogen affecting mostly goats, sheep and cattle. While acute Q fever is usually self-limiting and manifests itself as acute pneumonia or hepatitis, patients with chronic infection typically have endocarditis. However, in about 10%, vascular structures such as aneurysms or vascular grafts can be affected. Presumably, our patient first suffered from acute Q fever pneumonia. In the course of her illness, the aortic aneurysm was seeded with bacteria and chronic infection developed. The recommended treatment of chronic Q fever is doxycycline and hydroxychloroquine, for at least 18 months. Our patient, who refused taking hydroxychloroquine, is treated with doxycycline alone since almost two years and is doing well. Since she denied any animal contact, it is unknown how she got exposed to the organism.
The "Q" in Q fever stands for "query" (investigation). Since Q fever is not a common disease and symptoms are non-specific, the query for the right diagnosis can be long and difficult, as it was in our patient.



[A]

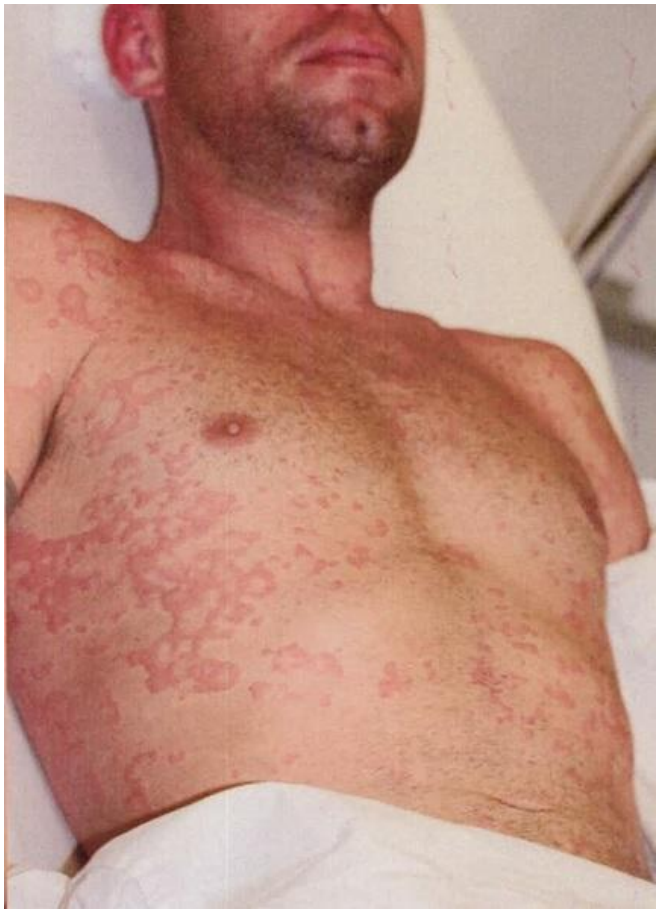


[B]

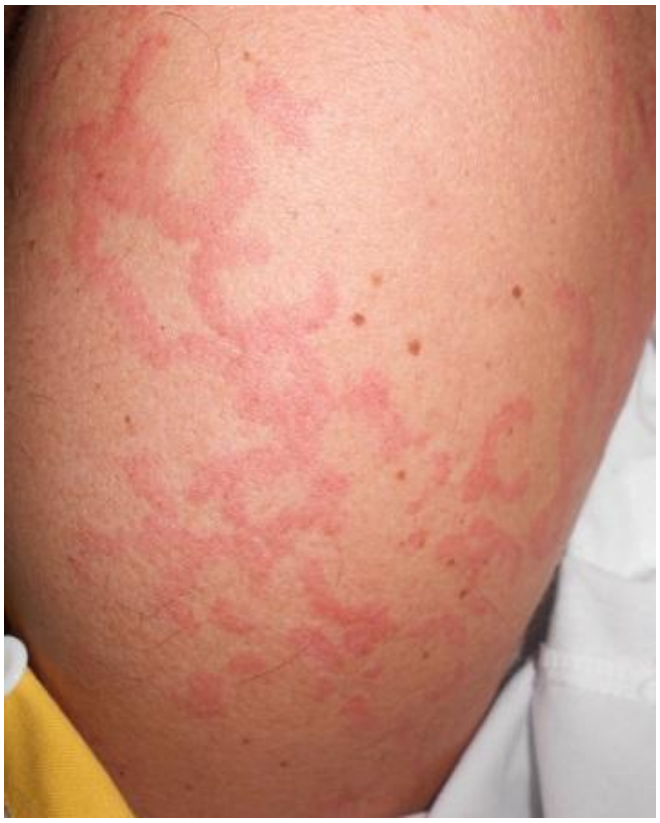
P414 **Primary herpes simplex virus type 1 infection can lead to prolonged pain induced general pseudoparesis**

Verena Charlotte Wilzeck[1], Alex Gysi[1], Jürg Hans Beer[1,2], Reshma Saskia Autar[1,3]
[1]Department of Medicine, Cantonal Hospital of Baden, Baden, [2]Laboratory for Platelet Research, Center for Molecular Cardiology, Schlieren, [3]Department of Infectious Diseases Cantonal Hospital Baden, Baden, Switzerland

Introduction: Herpes simplex virus type 1 (HSV-1) infection is typically acquired in early life. Primary infections are usually asymptomatic or accompanied by mild symptoms. Severe symptomatic HSV-infections in adult patients are uncommon.
Case report: A 30-year old male presented with an itching annular exanthema. Initially, he was diagnosed with an anaphylactic reaction and consequently treated with prednisone and antihistaminics, which lead to a transient improvement. Three days later he was admitted with a right-sided hemiparesis accompanied by myalgia, slight headache and persistence of the exanthema. Shortly after the admission, the paresis advanced to the left side, while the patient complained about severe muscle pain. He showed neck pain and -stiffness and articular effusions of the finger joints and knees. A few days later he developed blisters on the lips. Routine laboratory diagnostic was unremarkable. Cerebrospinal fluid analysis (CSF) showed a slightly elevated protein and glucose levels. Further investigations with brain and cervical cord MRI scans, nerve conduction velocity and electromyography were normal. Serological tests revealed positive IgM-antibodies for HSV-1 and -2 and positive HSV-1 IgG-antibodies. A PCR, taken from the lip blisters, was positive for HSV-1.
The diagnosis of a HSV-1 primary infection with erythema multiforme annulare and pain-induced pseudoparesis was made and an oral antiviral therapy with Valaciclovir was started. The patient received extended analgetic treatement including opioids. Within few days he showed increasing improvement of the paresis and a regression of the rash. The patient could be discharged after 4 days and did not show any residual neurological symptoms.
Discussion: HSV-1 primary infection usually affects skin and mucous membranes. However it can be accompanied by generalized symptoms such as myalgia and headache. To our knowledge this is the first case of a primary HSV-1 infection leading to general pain induced pseudoparesis. We found no evidence of an inflammatory or infectious myelitis or neuritis. Although HSV-IgM could persist after a previous HSV infection, the combination of clinical findings together with a negative HSV-2 IgG and positive HSV-1 PCR make, that we consider it a primary infection.
Conclusion: Primary HSV-1-Infection may lead to severe, generalized symptoms like transient pain-induced pseudoparesis.



[Erythema annulare]



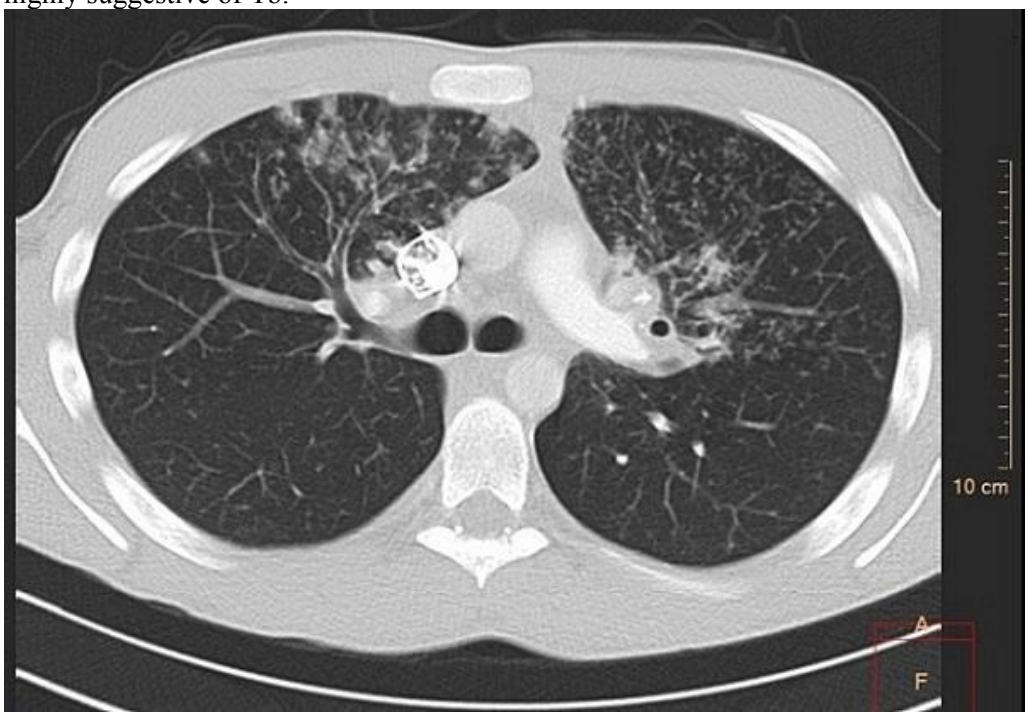
[Erythema annulare]

P415 Tree-in-bud sign: bronchogenic spread of tuberculosis

Bianca Roth[1], Helmut Rasch[2], Sebastian Wirz[3], Elke Ullmer[4]
[1]Medical University Clinic, [2]Department of Radiology, Kantonsspital Baselland, Bruderholz, [3]Division of Infectious Diseases, [4]Pulmonary Medicine, Med. Univ. Klinik, KSBL, Bruderholz, Switzerland

Background: Following decades of retreat, pulmonary tuberculosis (Tb) is once again gaining importance. Radiographic imaging plays a major role in the initial evaluation, followed by bacteriological confirmation. Typical patterns on CT scan may help to differentiate latent from active Tb.
Case: A 21-year-old Syrian male was admitted with cough, fever 39,2°C, weight loss, and progressive weakness over 3 weeks. Leucocytes (16.2 G/L) and CRP (70 mg/l, no < 5) were elevated. CT scan demonstrated patchy consolidations with cavitation in both upper lobes, bronchial wall thickening, and peripheral centrilobular nodules with concomitant Y- and V-shaped branching opacities (tree-in-bud sign). Bronchoalveolar lavage showed neutrophilic inflammation with acid-fast-bacilli, and PCR for mycobacterium tuberculosis complex was positive. A therapy with RIMSTAR® (rifampicin, isoniazid, ethambutol, pyrazinamide) was initiated.
Discussion: Tb is aerosol transmitted with the lung being the major site for primary infection and disease. In post-primary Tb, hematogenous, lymphatic, endobronchial or direct spread are possible and are accompanied by cough, fever, night sweats or weight loss.
The smallest component of the lung is the secondary pulmonary lobule. The bronchiole (< 1mm) and arteriole in the center of every lobulus, are not usually visible on CT scan. Histologically Tb shows caseating necrosis and granulomatous inflammation within and around the small airways. TIB is most pronounced in the lung periphery, but spares the pleural space. Together these factors produce a typical HR-CT pattern known as TIB where dilated, pus filled centrilobular bronchioles resemble a budding tree.
Initially described for the active endobronchial spread of Tb, this pattern may also be seen in other diseases with inflammation of the small airways, including infections with other pathogens, congenital disorders, aspiration, immunologic, and neoplastic disorders.

Conclusion:
-TIB represents inflammation of the small airways, histologically known as “bronchiolitis”
-In patients with pulmonary Tb, TIB is the most characteristic CT feature of active endobronchial spread and can be found in 72% of patients with active disease. TIB is suggestive for open Tb so that patients should be isolated and treated until microbiological results are available.
-TIB is not specific for Tb, but associated radiological features such as cavitation or patchy infiltrates are highly suggestive of Tb.



[Tree in bud]

Postertour 3

Infektiologie / Immunologie / Rheumatologie 2

Infectiologie / Immunologie / Rhumatologie 2

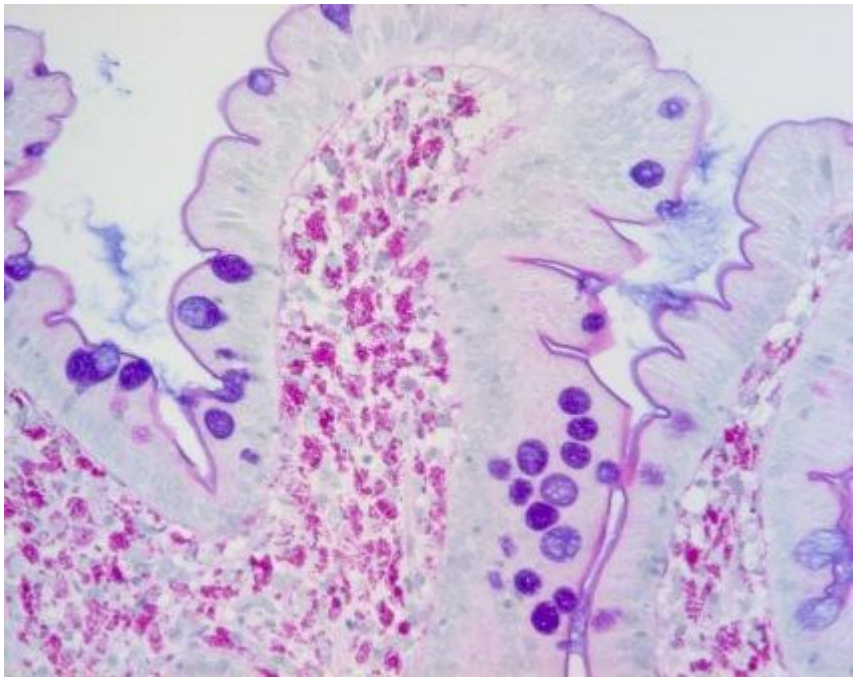
P416 15 years of follow up in a patient with Whipple´s disease

Markus Schneemann, Gabriele Schoedon
UniversitätsSpital Zürich, Klinik und Poliklinik für Innere Medizin, Zürich, Switzerland

We describe a Caucasian Swiss patient with severe weight loss, night sweats and hepatosplenomegaly who had been diagnosed with disseminated Whipple´s disease in a splenectomy specimen in 1999 at 42 years of age which was obtained in the workup of suspected lymphoma (Walter et al., Br J Haematol. 2001;112:677). Histopathology of the spleen showed strongly positive particles inside macrophages in a diastase-resistant periodic acid Schiff base staining (d-PAS). Duodenal biopsies were d-PAS positive and reacted Tropheryma whipplei (Tw) - specific PCR. We decided to treat him with oral cotrimoxazole b.i.d. as long as histopathology remained positive in regularly performed duodenal biopsies. Clinically, the patient had improved rapidly, gained weight and was asymptomatic since the year 2000. In 2007 the biopsies were d-PAS negative, but, interestingly, “foamy cells” were still present. Tw - specific PCR was negative. We stopped the antibiotics after eight years of treatment! In 2012, another control endoscopy comfirmed d-PAS and PCR negative biopsies. The rationale for longterm treatment is the following: 1) the macrophages of patients with Whipple´s disease display a yet ill defined incapacity to kill Tw that is supposed to be permanent. 2) the ubiquitous nature of Tw in the environment. Therefore, longterm antibiotic treatment is

both therapy of Whipple´s disease plus prophylaxis against reinfection in a vulnerable host. Therefore, after antibiotics were stopped, we continue to control the patient on a once-a-year basis for clinical signs of recurrence / reinfection, i.e. weight loss, diarrhea, fever, and a endoscopy with duodenal biopsies every five years to check for subclinical recurrence of Tw in d-PAS and Tw specific PCR.

Based on these pathophysiological considerations we have arranged longterm follow up of several patients with confirmed Whipple´s disease in our clinic to prevent potentially fatal relapses of Whipple's disease and improve out knowledge about this fascinating disease.



[WhippleDarmB]

P417 Fever and sacroiliac pain: think systemic brucellosis!

Wulf Daniel Winkler, Dennis Storz, Philip Tarr
University Clinic of Internal Medicine, Kantonsspital Baselland, Bruderholz, Switzerland

Case report: A 58-year-old woman presented to her family doctor with asthenia, lower back pain and right sided flank pain. She was treated with antibiotics for presumed urinary tract infection on 2 occasions. The pain persisted, however, for more than 2 months and she presented to the emergency room when chills and fever developed. The patient had a history of dilatative cardiomyopathy; an implantable cardioverter-defibrillator had been implanted 3 years prior to admission. On admission, a temperature of 39.5°C, tachycardia and hypotension were noted. Physical examination was normal except for tenderness in the right sacroiliac area during sacroiliac maneuvers.
Hospital course: Laboratory analyses showed a C-reactive protein level of 73 mg/l, with a normal erythrocyte sedimentation rate. Blood cultures grew *Brucella melitensis*. Brucella agglutinin test was positive. Transesophageal echocardiography did not reveal any abnormalities. On further questioning, the patient was born in Anatolia (Turkey). She immigrated to Switzerland 40 years ago, but regularly spends her vacation in rural Anatolia (last visit, 3 months prior to admission), where she regularly ingests fresh, unpasteurized goat milk. Clinical response was excellent to antibiotic treatment with rifampicin (450mg once daily) and doxycycline (100mg twice daily) for 3 months. Intravenous gentamicin (5mg/kg daily) was given for the first 7 days given the presence of an endovascular foreign body.
Discussion: This patient presented with symptoms and signs of systemic (fever, asthenia) and focal brucellosis (sacroiliac pain). Osteoarticular manifestations including sacroileitis are the most common form of focal brucellosis. It is unclear if the manifestations in our patient were due to recent brucellosis acquisition

because brucellosis is well known to reactivate years after initial, successfully treated infection. In 2010, we described focal reactivation of brucellosis 28 years after initial infection. Given the rarity of brucellosis (3-4 cases/year in Switzerland in last 3 years) this case highlights the importance of considering this diagnosis in the evaluation of migrants with fever of unclear source, based on accurate travel and dietary history.

P418 Newly diagnosed Sjögren's syndrom leading to false positive malaria testing

Julia Freibrodt[1], Andrée Friedl[1,2], Hans-Ruedi Schmid[1], Jürg Hans Beer[1,3], Alex Gysi[1]
[1]Department of Internal Medicine, Cantonal Hospital Baden, [2]Department of Infectious Diseases Cantonal Hospital Baden, Baden, [3]Laboratory of Platelet Research, Molecular Cardiology, University of Zurich, Schlieren, Switzerland

Introduction: Malaria is a mosquito-borne disease in the tropics. Malaria rapid diagnostic tests play an important role in its diagnosis.
Case report: We report a 74 year old patient who suffered from symptoms of a common cold with productive cough and fever while he was on holidays in India. He had been treated with amoxicillin-clavulanate, which had not improved his fever. Initially we found a febrile (38.4°C), tachypneic patient with pulmonary rales on the right lower lung side. Laboratory findings were normal (Leucocytes 6700/µl, CRP 2 mg/l, Hb 12.4 g/dl, Tc 237000/µl) as well as a chest X-ray. Based on the history with mosquito bites in India a malaria rapid diagnostic test (BinaxNOW®) was done, which was slightly positive. Treatment with Artemether/Lumefantrin was initiated. Serologies for Chickungunya, Rickettsia and Dengue, PCR for Influenza and blood cultures remained negative. Surprisingly the blood films showed no plasmodia. In subsequent additional PCR-testing no plasmodia DNA was detected. Because the patient had been investigated for a falsely positive screening Immunoassay test (HIV Combo Test) in the past and because of persistent fever, we searched for an underlying cause. Urine and serum electrophoresis were negative, however the rheumatoid factor was positive (347 U/ml), and titers for ANA (1:1280) and Sjögren's Syndrom A SSA/Ro60 (>1:1300) were increased. The patient reported distinctive sicca symptoms (mouth, eyes) for a few months. We therefore suspect that Sjögren's Syndrome was the cause of his fever.
Discussion: The patient was treated with Artemether/Lumefantrin since malaria was suspected because of a positive rapid test. The BinaxNOW® test is an immunochromatographic membrane assay that uses monoclonal antibodies to detect Plasmodium falciparum antigen and pan-malaria antigen. Studies have shown a sensitivity of 93-97% and a specificity of 93-95%. Samples with positive rheumatoid factor titers may produce false positive results (up to 8%). Microscopic examinations of blood films remain the gold standard for the diagnosis of malaria. To exclude malaria it is possible to specifically detect the DNA of plasmodia by PCR.
Conclusion: Rapid tests simplify clinical practice, allow diagnosis of for example malaria by personnel untrained in reading blood films for malaria and allow early initiation of therapy. Nevertheless, the tests are only tools, so other features of specific diseases should not be disregarded.

P419 An unusual cause of dyspnea

Joana Vieira Barbosa[1], Caroline Zosso[1], Olivier Lamy[1], Pierre-Alexandre Bart[1], Catherine Beigelman-Aubry[2], Romain Lazor[3], Francois Spertini[4]
[1]Department of Internal Medicine, [2]Department of Radiology, [3]Department of Pneumology, [4]Department of Immuno-allergology, CHUV, Lausanne, Switzerland

Introduction: Dyspnea is one of the leading causes of hospitalization in a service of internal medicine. The etiology is diversified and complex and a systematic approach can help identify uncommon causes. Sjögren's syndrome (SS) is a systemic autoimmune disease that affects 0.2 to 3% of the population. Interstitial lung disease (ILD) is the most common pulmonary abnormality in SS with prevalence varying from 9 to 75%, depending on criteria used. However, presentation is not always typical.
Case report: We report the case of a 79 year-old woman presenting to our emergency department with new onset dyspnea class III-IV NYHA, orthopnea and cough. Physical examination was remarkable for signs of

fluid overload and inspiratory crackles. A chest radiography showed bilateral interstitial infiltrates and signs of heart failure. Despite treatment with intravenous furosemide, clinical course was marked by persistent and severe hypoxemia (pO2 40mmHg while breathing ambient air). Transthoracic echocardiography revealed normal left ventricle function, while pulmonary hypertension was estimated at 56 mmHg. A chest scan demonstrated bilateral areas of diffuse ground-glass attenuation, patchy alveolar consolidation and honeycombing compatible with nonspecific interstitial pneumonia (NSIP). A bronchoscopy showed a predominance of lymphocytes, neutrophils and eosinophils in the bronchoalveolar lavage.
Retrospective study of medical records, revealed a positive antinuclear antibody titer (ANA 1:1280) with an anti-Ro/SSA and anti-La/SSB pattern, a positive rheumatoid factor, as well as a positive Shirmer test performed one year earlier in the context of a "sicca complex". The diagnosis of NSIP as a manifestation of extraglandular SS was retained and treatment with prednisone was initiated.
Conclusion: Our case reminds the importance to recognize the clinical features associated with extraglandular SS. Diffuse ILD is the most serious form of lung involvement, and clinical course is usually slowly progressive or even asymptomatic. This case illustrates a rapid progressive ILD as the first systemic manifestation of a SS, which is an atypical type of presentation with only one case described in the literature. Diagnosis remains challenging in the clinical practice especially in polymorbid patients and keeping a high index of suspicion plays a paramount role in patient care.

P420 Retroperitoneal lymphadenitis and psoas abscess due to Mycobacterium avium in a patient with chronic lymphocytic leukemia treated with obinutuzumab

Bettina Strohdach[1], Anna L. Falkowski[2], Nicolin Hainc[2], Philippe Brunner[3], Matthias Stahl[1], Lorenz Jost[1], Philip E. Tarr[1]
[1]Innere Medizin, Kantonsspital Baselland, Bruderholz, [2]Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel, [3]Pathologie, Kantonsspital Baselland, Liestal, Switzerland

Background: Infection with mycobacterium avium complex (MAC) occurs infrequently and in largely two settings. First, as pulmonary infection, typically in elderly women who are otherwise healthy, and as often disseminated disease in patients with severe cellular immunodeficiency.
Case report: A patient, born in 1940, had chronic lymphatic leukemia (CLL) diagnosed in 2000, and was treated for generalized extensive nodular involvement with numerous agents during 13 years. In December 2013, progressive clinical symptoms were attributed to progressive CLL, and monthly infusions of obinutuzumab were started. In May 2014 he developed extensive right retroperitoneal lymphadenitis complicated by a psoas abscess extending to the groin. Histological examination of a biopsy specimen of the abscess showed granulomatous inflammation and cultures grew Mycobacterium avium. Response was favorable to therapy with rifampicin, ethambutol and clarithromycin and external drainage of the abscess.
Discussion: Infectious complications are a well recorded complication in patients with CLL, typically presenting as pneumonia and bacteremia caused by encapsulated bacteria. To our knowledge, there are four other published cases of M. avium infection in CLL patients, highlighting the possible roles of the immunosuppression due to the CLL and due to complications of its therapy. A potential of obinutuzumab to cause severe cellular immunodeficiency has not previously been recorded in clinical trials of this agent in CLL. Recognition of MAC infection in our patient was delayed because progressive CLL was suspected as the cause of increasing retroperitoneal adenopathy - MAC infection was only diagnosed when the newly appearing groin mass was biopsied.

P421 Prognostic value of procalcitonin in respiratory tract infections across clinical settings

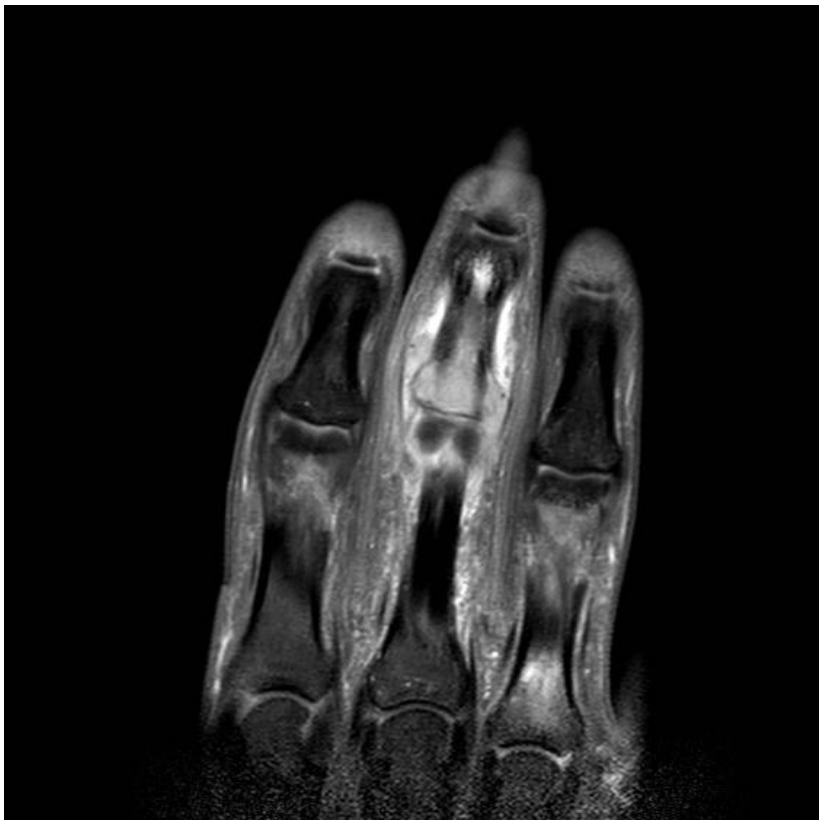
Alexander Kutz, Beat Mueller, Philipp Schuetz, for the IPD Study Group
Allgemein Innere Medizin, Medizinische Universitätsklinik, Kantonsspital Aarau, Aarau, Switzerland

Introduction: Whether the inflammatory biomarker procalcitonin provides prognostic information across clinical settings and different acute respiratory tract infections (ARI) is poorly understood. Herein, we investigated the prognostic value of admission procalcitonin levels to predict adverse clinical outcome in a large ARI population.
Methods: We analysed data from 14 trials and 4211 ARI patients to study associations of admission procalcitonin levels and setting specific treatment failure and mortality alone at 30 days. We used multivariable hierarchical logistic regression and conducted sensitivity analyses stratified by clinical settings and ARI diagnoses to assess the results` consistency.
Results: Overall, 864 patients (20.5%) experienced treatment failure and 252 (6.0%) died. The ability of procalcitonin to differentiate patients with and without treatment failure was highest in the emergency department setting (treatment failure; area under the curve (AUC): 0.64 (95% confidence interval [CI]: 0.61, 0.67), adjusted odds ratio (OR): 1.85 (95% CI: 1.61, 2.12), $p< 0.001$ - mortality; AUC: 0.67 (95% CI: 0.63, 0.71), adjusted OR: 1.82 (95% CI: 1.45, 2.29), $p< 0.001$). In lower respiratory tract infections, procalcitonin was a good predictor of identifying patients at risk for mortality (AUC: 0.71 (95% CI: 0.68, 0.74), adjusted OR: 2.13 (95% CI: 1.82, 2.49), $p< 0.001$). In primary care and intensive care unit patients no significant associations of initial procalcitonin levels and outcome was found.
Conclusions: Admission procalcitonin levels are associated with setting specific treatment failure and provide most prognostic information in ARI in the emergency department setting.
Reference: Schuetz P. et al. CID 2012

P422 A swollen finger and subcutaneous nodules - an unusual presentation of sarcoidosis

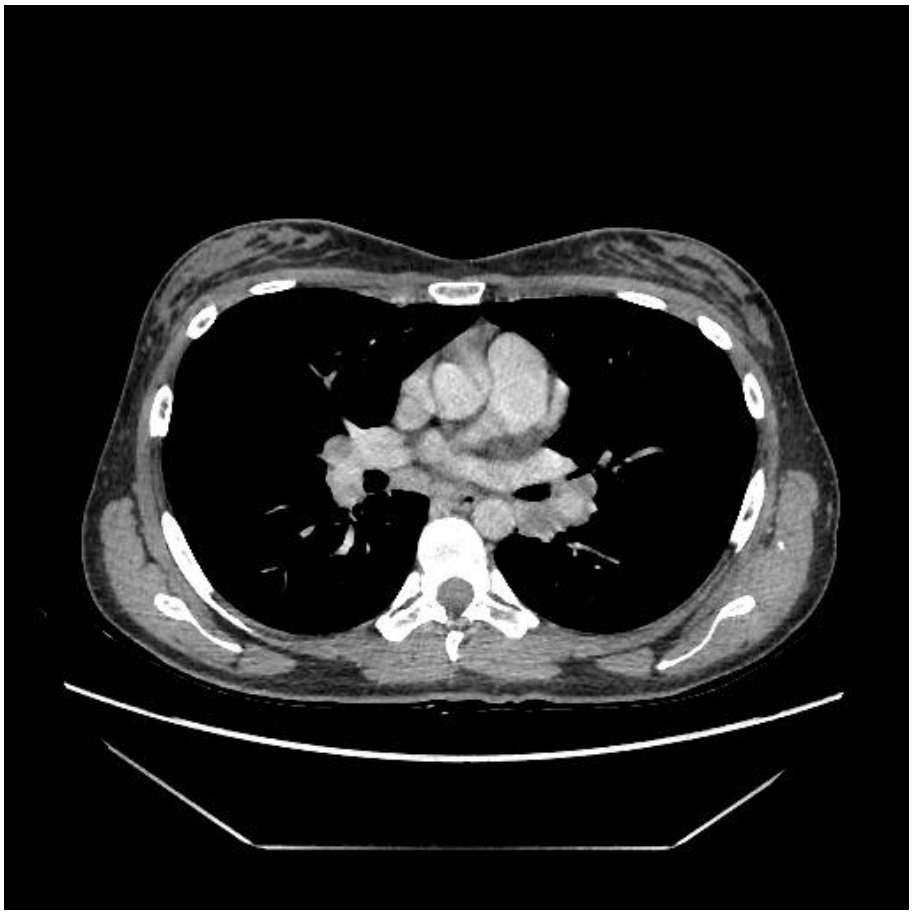
L. Meyer[1], S. Richner[1], S. Ali[2], C.A. Meier[1], I. Laube[1]
[1]Department of Internal Medicine and Specialities, [2]Division of Pathology, Triemli Hospital, Zurich, Switzerland

Introduction: Sarcoidosis is a chronic illness of unknown etiology, characterized by non-caseating granuloma affecting different organs. Most cases (90-95%) present with pulmonary involvement. We here report a case of mainly extrapulmonary sarcoidosis. **Case:** A 27-year-old woman presented with painful swelling of the right middle finger with undulating fever since four weeks. The initial antibiotic treatment for suspected phlegmonous infection did not improve the symptoms and a broad work-up (HIV, rheumatoid factors, anti-CCP, ANA, anti-dsDNS, ENA-Screen) was negative. MRI of the digit was highly suspicious of a malignant process, e.g. lymphoma, Ewing sarcoma.



[MRI Hand rechts]

At hospital admission clinical examination showed an indolent subcutaneous nodule on the left forearm. Similar nodules of the right arm were previously excised in another hospital for aesthetical reasons. Histologically, a chronic lymphoplasmacellular and granulomatous inflammation with epitheloid-cell granuloma was seen. A CT-scan of the chest and abdomen showed bilateral hilar and mediastinal lymphadenopathy.



[CT Thorax]

Together with the bone and skin involvement, sarcoidosis was suspected which could be confirmed by biopsies of respiratory mucosa showing similar non-caseating epitheloid-cell granuloma with giant cells. In the differential diagnosis we considered foreign body granuloma based on temporal coincidence with a new tattoo; however, histologically there was no evidence of ink traces. Tuberculosis was excluded. There was no indication for systemic steroid therapy due to normal pulmonary function and CO diffusion capacity and the absence of pulmonary symptoms. The arthritis was initially treated with NSAIDs, but glucocorticoids, methotrexate and hydroxychloroquine had to be added to relieve the symptoms.

Discussion: Sarcoidosis has a very variable clinical manifestation. Up to 30% of patients present with extrapulmonary sarcoidosis. Cutanous lesions are seen in about 25% of patients, whereas bone involvement is relatively rare (1-13%). The diagnosis of sarcoidosis can be made with the presentation of typical clinical symptoms (e.g. bilateral hilar lymphadenopathy) and/or radiological characteristics together with the histological evidence of non-caseating epitheloid-cell granuloma. First-line therapy is usually corticosteroids.

Conclusion: Sarcoidosis should be considered in patients presenting with affection of different organs and general symptoms, even if there is no obvious pulmonary involvement.

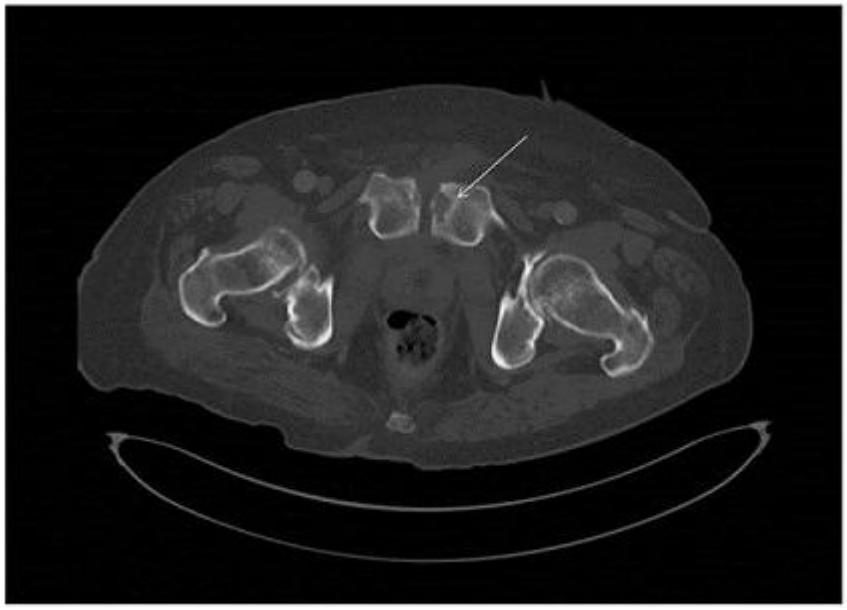
P423 Nach dem ESBL im Urin die weisse Pest in Knochen, Urin und Pleura

Sevdjane Mustafa, Philippe Rochat, Beat Frauchiger
Kantonsspital Frauenfeld, Frauenfeld, Switzerland

Einleitung: Mit jährlich ca. 9 Millionen Erkrankungen und einer Prävalenz von ca 30% (meist latente Form) der Weltbevölkerung ist die Tuberkulose (Tbc) weltweit die häufigste Infektionskrankheit. Die Inzidenz in der Schweiz war in den letzten 100 Jahren abnehmend. Die meisten Fälle betreffen junge Immigranten mit einer Primärinfektion. Auch Personen Schweizer Herkunft können betroffen sein, zumeist mit einer Reaktivierung im höheren Alter.

Fallbeschreibung: Die Zuweisung des 78-jährigen Patienten erfolgte zur Abklärung eines persistierenden Entzündungszustands nach Behandlung eines Harnwegsinfektes mit ESBL-produzierenden Klebsiella pneumoniae in Spanien.

Klinisch und konventionell-radiologisch fand sich ein Pleuraerguss rechts. Laboranalytisch bestanden erhöhte Entzündungsparameter (CRP 68 mg/l, BSR 96 mm/h) und eine normochrome, normozytäre Anämie (Hb 96 g/l). Eine persistierende Leukozyturie war steril.
Bei Schmerzen im Schambeinastbereich fand sich in der CT des Thorax und Abdomens ausser dem bekannten Pleuraerguss rechts eine Osteolyse im symphysennahen Os pubis (Abb. 1).
Das Pleurapunktat ergab ein Exsudat (2'111 Lc/µl, 98% mononukleär) und ein erhöhtes IFN-Gamma (282 ng/l). Die Mikroskopie und Kultur des Pleurapunktates und des Sputums waren negativ für Mykobakterien.
In der CT-gesteuerten Biopsie des Os pubis fand sich nekrotisches Gewebe mit granulozytärer Entzündung und epitheloidzelligen Granulomen ohne Keimnachweis. In einer offenen Knochenbiopsie und später im Urin konnte M.tuberculosis in der PCR und in der Kultur gefunden werden.
Somit handelte es sich um eine Knochen-, Urogenital- und Pleura-Tuberkulose. Es wurde eine Vierertherapie mit Isoniazid, Rifampicin, Ethambutol und Pyrazinamid für 2 Monate begonnen. Die Gesamttherapiedauer wurde vorderhand für 6 Monate vorgesehen. Die Mycobakterien waren auf alle getesteten Antibiotika sensibel.
Kommentar: In den Jahren 2005 bis 2011 handelte es sich bei 21% der Fälle von Tbc bei Personen Schweizer Herkunft um einen extrapulmonalen Befall. Pleura (6.9%), Knochen (1.4%) und Urogenitaltrakt (2.7%) sind selten betroffen.
Wir gingen bei diesem Patienten von einer Reaktivierung einer latenten Tbc im Alter aus.
Trotz abnehmender Inzidenz in der Schweiz bleibt die Tbc auch an extrapulmonalen Lokalisationen differentialdiagnostisch bei uns eine Ursache von lokalen Pathologien. Retrospektiv stellt sich die Frage, ob der ESBL in Spanien oder damals schon die Tbc die Klinik erklärt hatte.



[CT Thorax/Abdomen vom 13.11.2014]

Postertour 3:

Infektiologie / Immunologie / Rheumatologie 3
Nephrologie / Arterieller Bluthochdruck

Infectiologie / Immunologie / Rhumatologie 3
Néphrologie / Hypertension artérielle

P424 Upper right abdominal pain and thrombosis of the inferior vena cava a case report

Kristina Rueegger[1], Konstantinos Karatolios[2], Philip Tarr[3], Jörg Humburg[4], Christina Jeanneret[2]
[1]Innere Medizin, [2]Angiologie, [3]Infektiologie, Med. Univ. Klinik, KSBL, [4]Klinik für Gynäkologie, KSBL, Bruderholz, Switzerland

We present a 26 year old female patient, who was admitted to the hospital because of an intense pain in the right upper abdomen. CT scan revealed a partially occluding thrombus in the inferior vena cava and a circular lesion in the liver segment VI. There was no swelling or pain of the legs. Laboratory analyses showed normochrome normocystic anaemia (haemoglobin, 110 g/l), a slight elevation of the gamma GT to 84 U/l as well as an elevation of C- reactice protein level of 38 mg/l. The D-Dimer level was 4.07 ug/l.
Follow up:
Anticoagulation with heparin iv was started. We found no signs of inferior venous cava congestion. A screening test for thrombophilia was unremarkable. Duplex sonography showed the wall adherent thrombus in the inferior vena cava with the upper edge reaching the confluence of the renal veins. The liver vein and the portal vein were not occluded. Ultrasound also revealed a circular liver lesion and a cystic mass of the left ovary which on MRI was compatible with a dermoid cyst). The patient was started on low molecular weight heparin. The ovarian mass was surgically removed (Histomorphology: cystic teratoma). Histopathological examination of an intraoperative biopsy specimen of the liver lesion showed granulomatous inflammation, and PCR was positive for Brucella spp., and negative for Mycobacterium tuberculosis and Bartonella spp. Anticoagulation was continued with low molecular weight heparin. Antibiotic treatment was started with Doxycyclin 100mg twice daily and Rifampicin 600mg once daily for 3 months, with Gentamycin 5mg/kg once daily iv given for the first 10 days.
On further questioning, the patient reported regular trips to rural Mexico, where she had eaten unpasteurized cheese from the local dairy farm. In retrospect she did not have any fever, but night sweats in the last 2-3 months. Follow-up duplexsonography of the vena cava showed normal venous flow without any residual thrombus after 7 months of anticoagulation treatment.
Discussion: To our knowledge, we present the first case of brucellosis-associated thrombosis of the vena cava. Vein thrombosis can be triggered by acute infections, which is well described e.g. in cytomegalovirus infection. The pathogenesis of deep vein thrombosis associated with brucellosis is not known. In summary, we describe a case of hepatic brucellosis and associated thrombosis of the inferior vena cava.

P425 Disseminated tuberculosis - think TB in 2015!

Alessandra Guaita[1], Esther Bächli[2], Christian Alfaré[2], Claudia Bütikofer[2]
[1]Medicine, [2]Spital Uster, Uster, Switzerland

Background: Disseminated tuberculosis (tbc) has become a rare diagnosis in the western civilization. 20 new cases were announced to the Swiss Federal Health Office in 2014. Between 1988 and 2014 there were 24.8 cases on average yearly. Due to the slow growth of mycobacteria and paucibacillarity in disseminated disease, the diagnosis of miliary tbc is difficult, despite new diagnostic tools developed in the last decades. PCR-Diagnostic tools allow diagnosis of M. tuberculosis faster.
Case: A 78 year old man with known atrial fibrillation presented with a 10 day history of respiratory tract infection with fever and cough, progressive dyspnoea and weight loss of 10 kg in two months. Two courses

of antibiotic regiments were unsuccessful. Bilateral rales were heard on chest examination. The clinical examination was otherwise unremarkable. Chest-X-ray showed fine reticular interstitial opacities and nodules. To specify the assumed interstitial pneumopathy we performed a CT-scan, which revealed parenchymal nodular granulomatous consolidations. Vasculitis, sarcoidosis, silicosis or miliary tbc was suggested. A bronchoalveolar lavage and a transbronchial biopsy confirmed necrotisising granulomas, but no presence of acid-fast-bacilli and negative PCR testing for M. tuberculosis. Laboratory studies revealed elevated CRP and pancytopenia. The bone marrow examination showed a granuloma with one acid-fast-bacillus and hemophagocytosis. Suspecting disseminated tbc we began a quadruple therapy. After three weeks mycobacterium tuberculosis bacilli were cultured from transbronchial biopsy and confirmed the diagnosis.

Conclusion: Disseminated tbc still exists, with constant number of cases since 1988 in Switzerland. We need to think about this rare but treatable disease. Diagnosis is still difficult, because PCR-tests are often negative. Therefore a culture of the bacillus remains gold standard. Because of paucibacillarity also normally sensitive PCR diagnostic tools (e.g. Cobas TaqMan MTB with sensitivity of 88.4% in respiratory specimens) may not help for a quick diagnosis (sensitivitiy of 63.6% in non-respiratory specimens).

P426 Prolonged fever and pancytopenia in a 40-year old woman: the diagnosis of the diagnostic process

Stéphanie Ribeiro[1], Ezequiel Rodríguez-Reimundes[2], Fang Cai[3], Laurent Christin[3], Jean-Francois Lambert[4], Marcos Schwab[3]

[1]Service de Médecine Interne, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, [2]Service de Médecine Interne Générale, Hôpitaux Universitaires de Genève (HUG), Genève, [3]Service de Médecine Interne et Soins Intensifs, Groupement Hospitalier de l'Ouest Lémanique (GHOL), [4]Service d'Oncologie-Hématologie, Groupement Hospitalier de l'Ouest Lémanique (GHOL), Nyon, Switzerland

Introduction: A 40-year-old Brazilian woman was admitted in a regional teaching hospital due to fever up to 40°C of 7 days duration. She had no relevant past medical history. Her heart rate was 113/minute and physical examination was otherwise unremarkable. Blood tests revealed pancytopenia (hemoglobin 90 g/l, leucocytes 2.3 G/l, platelets 113 G/l), slight elevation of liver enzymes and LDH, and increased C reactive protein (162 mg/l). Chest radiography and urine tests showed no alterations.

Blood cultures were sterile and fever persisted under empirical antibiotic therapy. As pancytopenia worsened, a conscious workup was warranted in order to rapidly achieve the correct diagnosis avoiding time consuming examinations.

Methods: The aim of this work is to describe the complex process of clinical reasoning that lead to successful diagnosis in this challenging and life-threatening case.

Results: Our initial strategic position was to identify and treat the most threatening diseases. Hence, we decided to start an empiric treatment for sepsis even if we had no evidence of a specific organ infection. Persistence of high fever and worsening pancytopenia as well as sterile cultures suggested a different origin. Serology for HIV, CMV, EBV, Parvovirus B19, and viral hepatitis were negative. Thoracic and abdominal CT-scanner showed a slight hepatosplenomegaly.

Hemophagocytic lymphohistiocytosis (HLH) was evocated. Ferritin blood levels were extremely increased. Bone marrow aspiration and biopsy confirmed this diagnosis.

Thorough reviews of HLH causes, as well as a meticulous review of the history with special attention the patient's country of origin, lead to the suspicion of visceral leishmaniasis. This was confirmed by positive serology for L. *infantum* as well as Leishmania's PCR in bone marrow specimen.

The patient was treated with liposomal amphotericin. Fever disappeared and blood cell counts increased achieving normal values within 3 weeks.

Conclusions: Clinicians unconsciously use multiple strategies to solve clinical problems, suggesting a high degree of mental plasticity in the diagnostic process.

Both intuitive pattern recognition and comprehensive analytical approaches were necessary to get to right diagnosis and to provide specific therapy. We believe that there is no substitute to clinical experience and that intuitive and analytical approaches occur simultaneously at all levels of clinical expertise.

P427 Acute abdomen caused by splanchnic vein thrombosis in idiopathic hypereosinophilic syndrome

Magdalena Stepien, Adrian Schmidt, Christoph A. Meier, Pascal Locher
Department of Internal Medicine and Specialities, Stadtspital Triemli Zürich, Zürich, Switzerland

Introduction: Hypereosinophilic syndrome (HES) can be defined as a systemic illness caused by an otherwise unexplained persistent eosinophilia (> 1.5 G/l) over several months leading to multiple organ damage and coagulopathy. We present a case of a young man with idiopathic hypereosinophilia, severe thrombocytopenia and a life-threatening hemorrhagic intestinal infarction due to splanchnic vein thrombosis.
Case report: A 21-year old man from Southern Asia presented at our hospital with a transient skin rash, intermittent abdominal pain, the first manifestation of hypereosinophilia (4.3 G/l) and severe thrombocytopenia of 13 G/l. Within two days the patient developed an acute abdomen due to hemorrhagic intestinal infarction caused by extensive splanchnic vein thrombosis as demonstrated by CT scan. These findings and the following serious complications were most likely caused by the persistent hypereosinophilia, which was also present in the bone marrow specimen. We interpreted the initial thrombocytopenia as a result of disseminated intravascular coagulation. Further clinical work-up revealed no cardiac or pulmonary involvement. With conservative treatment, platelet transfusions, and steroids (prednisone dosage of 1mg/kg for one week and afterwards reduction by 0.5mg/kg) we observed a clinical improvement; hence, intestinal resection could be avoided and the patient recovered without additional events. Our examinations did not reveal a clonal stem cell disorder (no cytogenetic aberration or molecular alterations for PDGFRα, PDGFRβ, FIP1L1-PDGFRα, FGFR1) or a secondary cause of hypereosinophilia (allergy, autoimmune disease, medication, parasitic and viral infections were all ruled out). A lymphoproliferative disorder was excluded by flowcytometry and mastocytosis by bone marrow examination.
Conclusions: Though hypereosinophilic syndrome (HES) is a rare hematological condition, its complications might be severe, especially due to abnormalities of coagulation. If not detected at early stage and treated properly, idiopathic hypereosinophilic syndrome can result in life-threatening complications. Except for clonal disorder (as e.g. FIP1L1/PDGFRA, which could be treated with imatinib), patients presenting with HES are treated with immunosuppressive therapy.

P428 Compliance with the European society of hypertension risk stratification guidelines in primary care - data from the Swiss hypertension cohort study

Anja Handschin[1], Andreas Zeller[2], Peter Tschudi[2], Benedict Martina[2], Jörg Leuppi[1], Thomas Dieterle[1]
[1]Medizinische Universitätsklinik, Kantonspital Liestal, Liestal, [2]Institut für Hausarztmedizin (IHAMBB), Universität Basel, Basel, Switzerland

Objective: Cardiovascular (CV) risk stratification in patients with arterial hypertension is essential for tailoring adequate antihypertensive treatment. Only few data is available on CV risk stratification in primary care patients with arterial hypertension. The aim of this sub-analysis from the Swiss Hypertension Cohort Study (HccH) was to evaluate the compliance of general practitioners with the ESH/ESC guidelines on CV risk stratification in arterial hypertension and to identify potential gaps in the risk stratification process.
Design and methods: HccH is an ongoing prospective observational study which has been initiated in 2005 by the Institute for Primary Care of the University of Basel, Switzerland. Data collection is conducted by general practitioners in Switzerland. Eligible patients are adult men and women (age >=18 years) with arterial hypertension. Inclusion criteria are antihypertensive treatment respectively a mean through sitting office blood pressure (OBPM) >=140/90mmHg. Patient characteristics, OBPM, CV risk factors, asymptomatic target organ damage (OD), diabetes (DM), chronic kidney disease (CKD) and symptomatic CV and renal disease are recorded on an annual basis and CV risk is analyzed according to the 2013 ESH/ESC Guidelines.
Results: Baseline data from 1005 patients included into HccH are given in the following table:

Parameters for CV risk stratification	Baseline data	Not recorded
Medical history, clinical risk factors		
Age [years]	68±13	0 (0%)
Gender [M/F]	M: 564 (56.1%) /F: 441 (43.9 %)	0 (0%)
OBPM systolic/diastolic [mmHg]	140±17 / 82±11	16 (1.6%)
ABPM systolic/diastolic [mmHg]	137 ± 14 / 83 ± 10	811 (80.7%)
Smoking status [Y/N/Ex]	147 (15%)/ 635 (64.6%)/ 201 (20.4%)	22 (2.2%)
Family history for CV disease	211 (36.7%)	430 (42.8%)
BMI [kg/m²]	28.5 ± 5.1	10 (1%)
Total cholesterol [mmol/L]	5.2 ± 1.1	351 (34.9%)
Fasting Blood Glucose [mmol/L]	6.2 ± 2.3	346 (34.4 %)
Waist circumference [cm]	102± 13	931 (92.6%)
Presence of OD		
Left ventricular hypertrophy	72 (13.3%)	471 (46.9%)
Microalbuminuria	33 (14.2%)	773 (76.3%)
GFR 30-60ml/min/1.73m	259 (33.9%)	241 (24.0%)
DM	276 (28.0%)	21 (2.1%)
Carotid plaques	3 (0.3%)	22 (2.1%)
Established CV / renal disease		
CV Disease (CHD, CHF, PAD, Stroke/ TIA)	209 (21.3%)	22 (2.1%)
Renal Disease (CKD stage>=4)	53 (6.9%)	241 (24.0%)

[Baseline]

Conclusion: Therapy in hypertensive patients should be based on an individual overall CV risk. Therefore, comprehensive risk stratification is mandatory. Our preliminary analysis from HccH demonstrates that most CV risk factors are recorded in primary care. However, substantial gaps were revealed with regards to the assessment of asymptomatic OD, particularly microalbuminuria and left ventricular hypertrophy. Consequently overall CV risk may be significantly underestimated in primary care patients with arterial hypertension.

P429 Kidney stone and carbonic anhydratase inhibitors- where is the link?

Cristina Elena Anghel, Thomas Bregenzer, Robert Schorn
Innere Medizin, Spital Lachen, Lachen, Switzerland

Introduction: The term renal tubular acidosis (RTA) refers to a group of disorders with an impaired net acid excretion leading to a normal anion gap acidosis. Three forms of RTA are known. Distal RTA (type 1) is characterized by impaired hydrogen ion secretion in the distal nephron. A reduced bicarbonate reabsorption in the proximal nephron causes proximal RTA (type 2), where as type 4 RTA is due to either aldosterone deficiency or tubular resistance to aldosterone. Carbonic anhydratase inhibitors can induce type 1 and 2 RTA.

Case report: A 55-year-old female patient was admitted with persistent right flank pain and pollakiuria. Her personal history was remarkable for pseudotumor cerebri, causing headaches and visual symptoms. The therapy included regular lumbar punctures and a medical therapy with Diamox® (acetazolamide) 2000 mg daily and Topamax® (topiramate) 100 mg daily, both started one year before. Physical examination

demonstrated right flank pain and suprapubic tenderness. Ultrasound and computer tomography confirmed bilateral nephrolithiasis (big staghorn calculus of the left side and a 1 mm calculus on the right side) as well as dexter hydronephrosis stage I-II. Laboratory results showed an impaired renal function (creatinine 101 µmol/l), normal anion gap metabolic acidosis (pH 7,3) and an alkalic urine (pH 8). The new diagnosed nephrolithiasis (normal CT-Scan two years before) associated with the non anion gap metabolic acidosis and alkalic urine lead to the diagnosis of a mixed RTA due to acetazolamide and topiramate. Topiramate and acetazolamide were stopped, but the latter had to be reintroduced because of visual symptoms. The metabolic acidosis partially resolved. Five weeks after discharge, extracorporeal shock wave lithotripsy was performed.
Discussion: Several medications can induce proximal and distal RTA including acetazolamide as well as topiramate leading to nephrolithiasis. Discontinuation of the medication and administration of potassium citrate will prevent new stone formation.
Conclusion: Patients receiving acetazolamide or topiramate should be evaluated for RTA and nephrolithiasis in a regular fashion.

P430 Electrolyte disorders and in-hospital mortality during prolonged heat periods: a cross-sectional analysis

Carmen Andrea Pfortmueller[1], Georg Christian Funk[2], Alexander Benedtik Leichtle[3], Georg Martin Fiedler[3], Christoph Schwarz[4], Aristomenis Konstantinos Exadaktylos[5], Gregor Lindner[6]
[1]Klinik für Allgemeine Anästhesie, Intensivmedizin und Schmerztherapie, Medizinische Universität Wien, Wien, [2]Department of Respiratory and Critical Care Medicine, Otto Wagner Spital Vienna and Ludwig-Boltzmann Institute for COPD and Respiratory Epidemiology, Vienna, Austria, [3]Center of Laboratory Medicine, University Institute of Clinical Chemistry, University Hospital and University of Bern, Bern, Switzerland, [4]Department of Nephrology, Landeskrankenhaus Steyr, Steyr, Austria, [5]Emergency Department, University and University Hospital of Bern, Bern, [6]Notfallzentrum, Klink am Park, Hirslanden AG, Zürich, Switzerland

Background: Heat periods during recent years were associated with excess hospitalization and mortality rates, especially in the elderly. We intended to study whether prolonged warmth/heat periods are associated with an increased prevalence of disorders of serum sodium and potassium and an increased hospital mortality.
Methods: In this cross-sectional analysis all patients admitted to the Department of Emergency Medicine of a large tertiary care facility between January 2009 and December 2010 with measurements of serum sodium were included. Demographic data along with detailed data on diuretic medication, length of hospital stay and hospital mortality were obtained for all patients. Data on daily temperatures (maximum, mean, minimum) and humidity were retrieved by Meteo Swiss.

Results: A total of 22.239 patients were included in the study. 5 periods with a temperature exceeding 25C for 3 to 5 days were noticed and 2 periods with temperatures exceeding 25uC for more than 5 days were noted. Additionally, 2 periods with 3 to 5 days with daily temperatures exceeding 30C were noted during the study period. We found a significantly increased prevalence of hyponatremia during heat periods. However, in the Cox regression analysis, prolonged heat was not associated with the prevalence of disorders of serum sodium or potassium. Admission during a heat period was an independent predictor for hospital mortality.
Conclusions: Although we found an increased prevalence of hyponatremia during heat periods, no convincing connection could be found for hypernatremia or disorders of serum potassium.

P431 Antihypertensive care in the very old aged 90 years and over: lessons form a survey in a German community hospital

Jürgen Bohlender[1], Jürg Nussberger[2], Beate Bohlender[3,4]
[1]Department of Nephrology and Clinical Pharmacology, University of Bern, Inselspital, Bern, [2]Département de Médecine, Service d'Angiologie, CHUV, Lausanne, Switzerland, [3]General Practice, [4]Klinikum Havelberg, Havelberg, Germany

Objective: The prevalence of hypertension increases dramatically with age while reliable data on antihypertensive care in the oldest patients aged >89 years are lacking. To get insight and improve the quality of hypertension care in these patients we analysed the characteristics, blood pressure (BP) and antihypertensive treatment of those admitted to a rural community hospital in Germany.
Method: All patients admitted to the medical ward aged >89 years (y) were prospectively included over a 12 months period ending in 2010. Within an extended cardiovascular risk profiling offered to those >59 y, patients had sitting BP taken at hospital admission with an ECG and blood tests; fasting serum lipid measurements were >2 days thereafter. Antihypertensive treatment followed German guidelines. Follow-up sitting BP was obtained in the morning before drug intake. Patients with septic or circulatory shock and re-admissions were excluded.
Results: N=58 patients aged 92±3 y (mean±SD; 90-101) with an average 11 (median; 4-32) in-hospital days were included (77.6% female, 34.5% diabetics, 24.1% atrial fibrillation, 41.4% coronary heart disease). Main diagnoses were diabetes mellitus, non-septic infections, heart insufficiency, orthopedic pain, and neuro-cognitive impairment. Admission systolic BP was 149±29 mmHg (n=16 >159 mmHg), diastolic BP 88±31 mmHg, heart rate (HR) 87±15/min, weight 62.1±11,6 kg, serum creatinine 112±48 micromol/l, total cholesterol 4.9±1.2 mmol/l, blood hemoglobin 7.8±1.2 mmol/l. Mid-term BP was 128±22/72±9 mmHg (HR 76±9/min). Discharge BP was 128±17/72±9 mmHg (none >159 mmHg) and HR 73±6/min (BP 21±43/17±35 mmHg and HR 16±22/min lower vs. admission; $p< 0.01$). Mean antihypertensives/patient (admission vs. discharge) excluding diuretics (D) was 1.0±0.9 vs. 1.1±0.9 (p=NS), including D 1.5±1.2 vs. 1.7±1,1 ($p< 0.05$): blockers of B-adrenoceptors 22.4% vs. 25.9%, Ca-channels 8.6% vs. 12.1%, the renin-angiotensin system (RAS) 63.8% vs. 63.8%; spironolactone 5.2% vs. 5.2%, others 1.7% vs. 3.4% (all p=NS); D 48.3% vs. 67.2% ($p< 0.05$); treated patients excluding D 67.2 % vs. 70.7% (any change 43.1%), including D 75.9% vs. 86.2%. There were no sex differences (p=NS).
Conclusion: Ambulatory BP treatment was usually by < 3 drugs, mainly adrenoceptor- and RAS-blockers or diuretics. Hospital discharge BP was well controlled while hospitalisation only increased the use of diuretics significantly.

Gastgesellschaft Postersession SFGG

Société conviée Session de poster SPSG

P432 My life story

Emilija Borizovski[1], Agathe De Chassey[2], Michel Sambuchi[2], Corine Farjon[2]
[1]Vaucluse, [2]CH Vaison la Romaine, Vaison la Romaine, France

Introduction: *"My life story"* is a concept which involves making a book of one's life inspired by individual experiences according to the Montessori Method.
In France since the 2nd January 2002 law came into action, it's compulsory to get every elderly person living in an old people's home to do a project which is about their personal life. Within our community, elderly people often need assistance and tend to be passive. Making a ´book of life´ enables them take control of their life story and memories and to come alive as individuals in order to be better cared for.
Method: The making of this personalized book "*My life story"* is a two-stage process. Firstly, information is collected from the elderly person and his/her family who will give a tale of the main events in their life by bringing personal pictures. Secondly, in the presence of the elderly person, there will be an activity workshop run by a pluridisciplinary team who will do a synopsis of his/her life trajectory. Each team member will collect specific information. Finally, the elderly person will give approval to the collection of information and communicate his/her expectations. Following this meeting, the book will be made. The elderly will then become the proud owner of a beautiful and easily readable album made of personal stories, pictures and memorable events in their life.
Results: The results are qualitative. We'll be measuring the positive effects of this book on the elderly person. It is important for this book to be a transitional object which will allow the elderly person to be connected to his/her environment. His/her active involvement in the making of this book will draw on his/her psyche and emotions. This will bring about ´intense´ emotions from the past which will help him/her to feel to feel even more alive. It will allow the person to be himself/herself again and improve his/her general health and self-esteem. It will make easily readable to the elderly person and will stay in his/her room in order to respect its confidentiality.
Conclusion: In order to prevent prescribing drugs, this book will allow the elderly person to find his/her dignity again but also to find a different way to communicate with the team. The benefits will be seen in the short and medium term. The book *"My life story*" will change the way we look at the dependant person and will encourage him/her to be a player of his /her past and present.

Gastgesellschaft SGH: Poster & Quick Oral Presentations

Société conviée SSH: Poster & Quick Oral Presentations

P433 Efficacy of ruxolitinib in the treatment of steroid-refractory graft-versus-host disease

Matyas Ecsedi[1], Sabine Gerull[1], Michael Medinger[1], Dominik Heim[1], Jakob Passweg[1], Claudia Lengerke[1,2]
[1]Clinic for Hematology, [2]Department for Biomedicine, University Hospital Basel, Basel, Switzerland

Introduction: morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Prognosis of disease not responding to primary treatment with corticosteroids is particularly poor. There is no standard therapy for steroid-refractory patients; Ruxolitinib is a selective JAK1/2 inhibitor currently in clinical use for the treatment of myeloproliferative neoplasms. Recently, JAK1/2 inhibition by ruxolitinib has been proposed for treatment of steroid-refractory GvHD (Spoerl et al, 2014). Demonstrated mechanisms of action were next to suppression of pro-inflammatory cytokine production also T-cell modulation (e.g. increase in regulatory T cells linked to immune tolerance).
Methods: Treatment with ruxolitinib was evaluated in five patients with steroid-refractory GvHD (4 acute,

one acute/chronic overlap syndrome following allo-HSCT for different indications that were treated with ruxolitinib between 04/2014 and 11/2014, after failure of one or more second line therapies.

Patient characteristics						
Patient nr.	**Disease**	**Donor**	**Gender**	**Age at GvhD occurence**	**GvHD:organ/grade at GvHD occurence**	**2nd line GVHD therapy**
1	Plasmacell myeloma	sibling	m	43	liver: III, skin: II	alemtuzumab
2	ALL	MMUD (9/10, HLA-A MM)	m	21	skin: II, liver: II, GI: IV	intra-arterial steroids, alemtuzumab
3	Plasmacell myeloma	MUD	m	55	liver: II, GI: IV	intra-arterial steroids, alemtuzumab
4	AML	sibling	m	66	GI: IV	intra-arterial steroids, alemtuzumab
5	T-prolymphocytic leukemia	MUD	m	41	overlap syndrome enoral: I, skin: II	extracorporal photopheresis

[Table 1, patient characteristics]

Results: GvHD involved the skin (n=3), liver (n=3), gastrointestinal tract (n=3) and the oral mucosa (n=1). Second-line treatment prior to ruxolitinib included tacrolimus (n=3), alemtuzumab (n=3), intra-arterial steroid application into mesenterial arteriess (n=2), cyclosporine (n=1), and ECP (n=1). All patients showed at least a partial response to ruxolitinib allowing reduction of steroid dosage, in three cases a complete response was observed, in 2 cases also after stop of the drug. Ruxolitinib was generally well tolerated despite the presence of cytopenias preexisting in all patients before treatment. A major concern in modulating T-cell activity is reactivation of latent virus infections such as cytomegalia virus (CMV). In three patients ruxolitinib was started while concurrent CMV replication was documented, this could be controlled subsequently using standard anti-viral treatment without cessation of ruxolitinib. Currently of the 5 patients 4 are alive, 1 died of progressive GvHD after cessation of ruxolitinib.

Response and follow-up					
Patient nr.	**Reduction of cortico-steroids after ruxolitinib**	**Clinical response**	**Time to response (weeks)**	**Duration of response (weeks)**	**Follow up (weeks)**
1	yes	CR	PR:1/CR:5	ongoing/10	10
2	yes	CR	PR:1/CR:2	ongoing/40	40
3	yes	PR	PR:3/CR:-	2/-	na
4	yes	CR	PR:1/CR:4	ongoing/-	11
5	yes	PR	PR:4/CR:-	ongoing/15	15

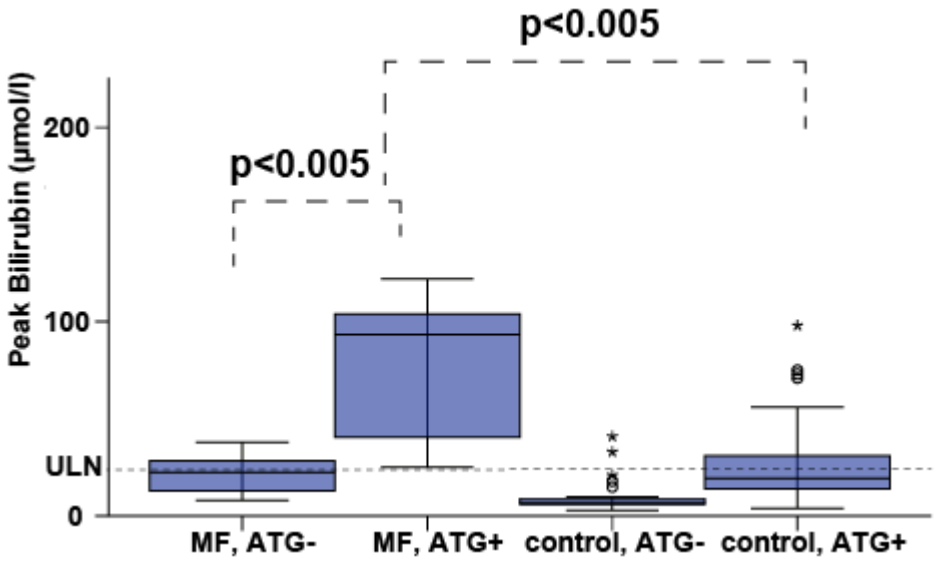
[Table 2, response and follow-up]

Discussion and conclusions: According to the results from this limited patient series, ruxolitinib treatment may be treatment option to be studied for the treatment of steroid-refractory GvHD.

P434 Enhanced hepatic toxicity in patients with myelofibrosis undergoing allogeneic hematopoietic stem cell transplantation and anti-thymocyte globulin treatment

Matyas Ecsedi[1], Jörg Halter[1], Michael Medinger[1], Jakob Passweg[1], Claudia Lengerke[1,2]
[1]Clinic for Hematology, [2]Departement for Biomedicine, University Hospital Basel, Basel, Switzerland

Introduction: Myelofibrosis (MF) is a myeloproliferative neoplasm associated with cytopenias, constitutional symptoms, hepatosplenomegaly and progression to acute leukemia. Currently, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative treatment for MF, but is restricted by mostly advanced age of MF patients at diagnosis. Inclusion of anti-thymocyte globulin (ATG) in conditioning regimens reduces the occurrence of acute graft-versus-host disease (GVHD), a major complication of allo-HSCT. Here, we explore whether ATG treatment may induce liver toxicity in MF patients typically presenting with active extramedullary hematopoiesis in this organ.
Materials and methods: Liver function parameters were evaluated during conditioning (until day 2 post-transplantation) with or without ATG, in patients undergoing allo-HSCT for MF at our centre between 2001 and 2014 (n=24) and as a control in patients receiving allo-HSCT for other indications between January 2013 and September 2014 (n=114).
Results: Addition of ATG to the conditioning regimen enhanced bilirubin in both patient MF and control patients (ATG + = 34,29 µmol, ATG- =11,83 µmol, $p< 10^{-6}$) while leaving ALAT, ASAT, alkaline phosphatase and GGT grossly unaltered. However, MF patients were significantly more susceptible to bilirubin increase upon ATG treatment, with 12/12 (100%) of MF patients versus 37/71 (52%) control group patients showing elevation of bilirubin (p=0.0051). We observed similar differences when restricted our analysis to a subgroup of patients receiving myeloablative conditioning (p=0.0095). In 7 cases of myelofibrosis patients receiving ATG, bilirubin differentiation was available, showing elevation of conjugated but not of unconjugated bilirubin. Liver ultrasonography carried out in 5 patients did not indicate visible cholestasis. In 50% of cases, bilirubin levels normalized within 7 days, in the remaining cases mild elevation persisted over longer periods of time.



[Peak bilirubin during conditioning]
Conclusion and Outlook: Our findings indicate that MF patients have a higher risk for cholestatic liver injury, which is further enhanced by treatment with ATG during allo-HSCT conditioning. The ATG-induced hepatic injury is self-limiting but may alter clearance of concomitantly applied drugs. We will present at the meeting data on an additional cohort of 27 patients with myelofibrosis treated with allo-HSCT at the University Medical Center Freiburg, Germany.

P435 High-dose chemotherapy with autologous stem cell transplantation is safe in myeloma and lymphoma patients > 65 years

Jasmin Stettler[1], Gabriela M. Baerlocher[2], Behrouz Mansouri-Taleghani[3], Urban Novak[1], Kurt Leibundgut[4], Thomas Pabst[1]
[1]Department für Medizinische Onkologie, [2]Department für Hämatologie, [3]Klinik für Hämatologie, [4]Department für Pädiatrische Hämato-Onkologie, Inselspital, Bern, Switzerland

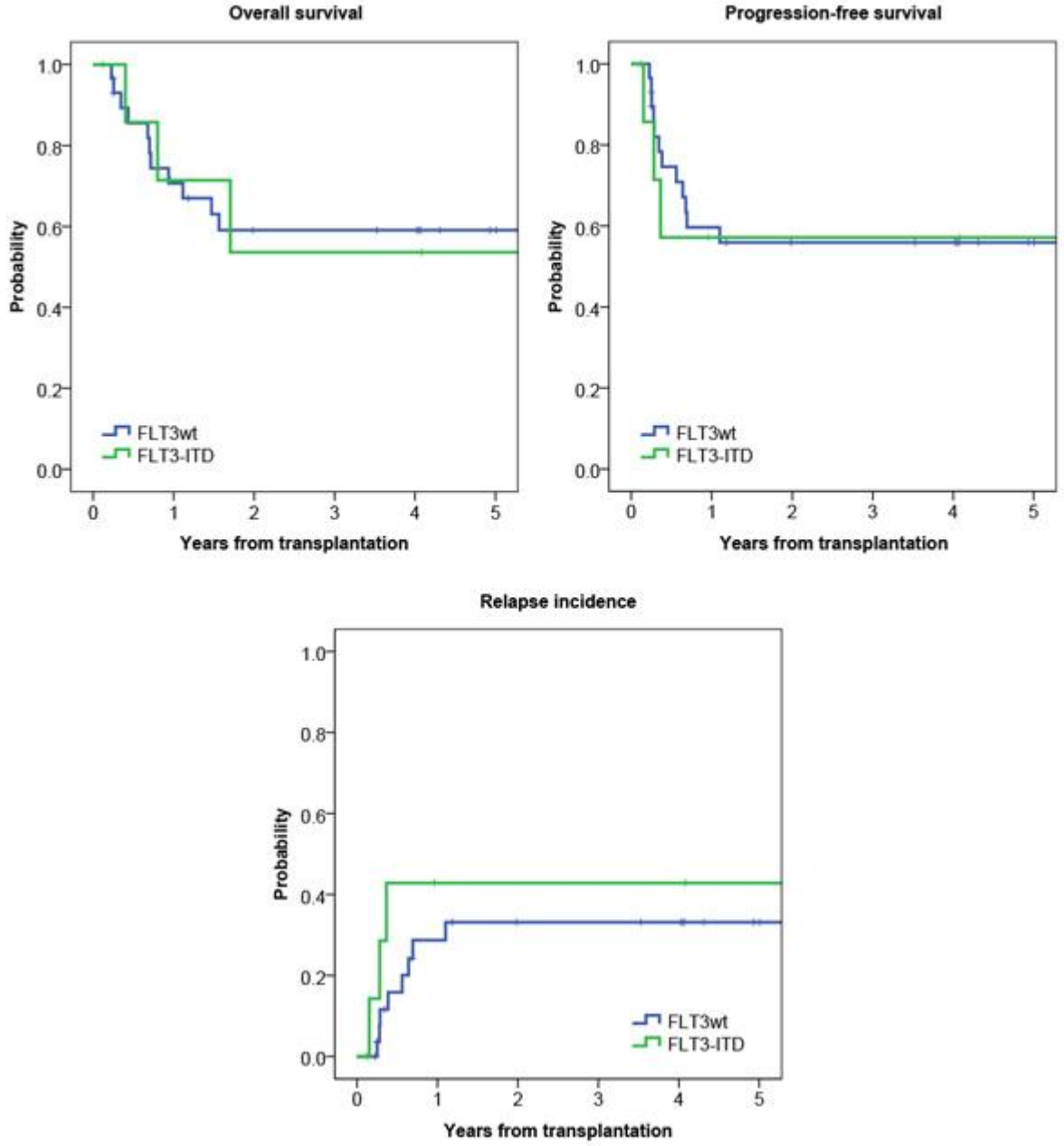
Background: For patients below 65 years with multiple myeloma or aggressive lymphomas, high-dose chemotherapy treatment (HDCT) with autologous stem cell transplantation (ASCT) is part of current standard treatment. However, tolerance and efficacy of HDCT in elderly patients >65 years are largely unknown, and such patients are usually not eligible for ASCT trials.
Methods: In this single-center study, we retrospectively analyzed safety and outcome of HDCT with ASCT in 370 consecutive patients treated between 01/2009 and 12/2013.
Results: We identified 65 patients undergoing HDCT with ASCT above the age of 65 years. These patients had a lower count of circulating CD34+ cells in the peripheral blood at the day of apheresis (P = .018) suggesting age-related decreased stem cell mobilizing potential. Age >65 years was not associated with increased transplant-related mortality within 100 days after ASCT. However, patients aged ≥ 70 years had prolonged duration of hospitalization (28.2 days versus 22.1 days; P = .0011). Noteworthy, myeloma patients aged ≥70 years had longer duration until platelet recovery (P = .0003). Finally, overall and progression-free survival rates one year after ASCT were not significantly different across the age cohorts.
Conclusion: Our data suggest that HDCT with ASCT for aggressive lymphomas or myeloma is feasible, safe and effective in patients older than 65 years. Age above 65 years *per se* should not exclude patients from HDCT with ASCT.

P436 Impact of FLT3-ITD mutations on the outcome of patients allografted with partial T-cell depleted grafts for AML in first complete remission with normal karyotypes

Yan Beauverd, Eddy Roosnek, Audrey Simon, Anne-Pascale Grandjean, Yordanka Tirefort, Carole Dantin, Olga Tsopra, Stavroula Masouridi-Levrat, Yves Chalandon
Hematology, Geneva University Hospitals, Geneva, Switzerland

Introduction: FLT3-ITD mutations are associated with poor prognosis in AML. Chemotherapy followed by HSCT is the treatment of choice because it increases overall survival (OS), progression-free survival (PFS) and decreases relapse incidence (RI) when compared with chemotherapy alone.
Partial T-cell depletion (TDEP) reduces GvHD incidence and may increase quality of life but may be associated with increased risk of relapse. Impact of FLT3-ITD mutations on outcomes has not yet been evaluated for partial TDEP in AML post-allogeneic HSCT.
Patients and methods: We analysed 37 consecutive patients allografted between 2003 and 2013, for AML with normal karyotype in first complete remission (CR1). 51% were female and median age was 55 years (range: 22-67). All patients were allografted with peripheral blood stem cells (PBSC) from identical siblings (35%), MUD (46%) and MMUD (19%). 54% of patients received a myeloablative and 46% a reduced intensity conditioning. Patients received grafts TDEP in vitro with CAMPATH-1H followed by an add-back of $100x10^6$/kg donor T cells on day +1. GvHD prophylaxis consisted of calcineurin inhibitor ± MTX, or MMF. We have compared 5-year OS, PFS and RI for patients with FLT3-ITD (n=8) and FLT3wt (n=29).
Results: 5-year OS for patients with FLT3-ITD was 54±40% and with FLT3wt was 59±19% (p=0.82). 5-year PFS for FLT3-ITD was 57±38% and FLT3wt was 58± 18% (p=0.89) and 5-year RI was 43±38% and 30±20% for FLT3-ITD and FLT3wt, respectively (p=0.43) (see figure 1). Acute GvHD grade 2-4 was experienced by 11% of patients and chronic GvHD by 16%.
Discussion: We did not observe differences in OS between FLT3-ITD and FLT3wt patients. Moreover, there is no increase of RI or decrease of PFS in patients with FLT3-ITD. These results suggest the feasibility of partial TDEP in CR1 AML with normal cytogenetic, without hampering outcomes. Moreover, use of partial TDEP reduces acute and chronic GvHD incidence, which may increase the quality of life of patients.

However our results should be interpreted with caution due to the low number of patients and the retrospective nature of the study and need to be confirmed in a largest prospective cohort.



[Figure 1]

P437 Fertility preservation in paediatric and adolescent patients in Switzerland - where do we stand today?

Tamara Diesch[1], Gabor Szinnai[1], Chistian De Geyter[2], Nicolas Xavier Von der Weid[1], Alicia Rovo[3]
[1]Universitäts-Kinderspital beider Basel, [2]Universitätsspital Basel, Basel, [3]Inselspital, Bern University Hospital, Bern, Switzerland

Infertility is a severe consequence of many cancer treatments with a major impact on quality of life of long term survivors. Advances in reproductive technologies enable some postpubertal patients to preserve fertility before the initiation of treatment for cancer. In prepubertal patients most options are considered

experimental. Despite a number of guidelines fertility preservation is not routinely discussed with paediatric patients and their parents. Aim of our study was to investigate the current stand on fertility preservation in Switzerland. We conducted a survey concerning fertility preservation counselling and applied fertility preservation measures (FPM) in all 9 paediatric oncological centres of Switzerland.

The questionnaire enclosing 24 questions was sent per mail to the respective heads of the Departments. All nine centres answered. Four (4/9) centres had a standardized program for fertility preservation. Two of them (2/4) for both pre- and postpubertal patients. The two other institutions (2/4) had a program only for postpubertal patients. In one half of the centres, counselling was by haematologist alone. Centres with an available SOP (N=4) offered an interdisciplinary counselling. Time point of counselling was within the first week of treatment. In the other centres no schedule was defined. The survey collected information regarding applied FPM in children and adolescents in 2013. The Swiss Childhood Cancer Registry reported in 2013 230 new cases of cancer in children and adolescents. In 125 (54%) of them FPM were performed. The most frequently applied technology in females was cryopreservation of ovarian tissue (19 prepubertal and 12 postpubertal girls). In boys, the most frequently applied method, was sperm banking (62 postpubertal boys). Lack of time and insufficient know-how were the most frequently mentioned reasons for not recommending and applying FPM.
In conclusion, this survey shows that fertility preservation counselling and measures are performed roughly in one half of paediatric oncological centres in Switzerland, leaving a large number of patients not taking benefit from this opportunity. Better education of the staff, introduction of a standardized algorithm, availability of structured time slots to perform FPM and financial support are needed to improve and facilitate the fertility preservation in paediatric oncology patients

P438 Comparison of three or fewer sequential high-dose chemotherapy cycles as salvage treatment in germ-cell tumors

Flavio Goessi[1], Martin Zweifel[1], Julian Schardt[1], Martin Spahn[2], George Thalmann[2], Thomas Pabst[1]
[1]Department für Medizinische Onkologie, [2]Department für Urologie, Inselspital, Bern, Switzerland

Background: Germ-cell tumors are highly curable with the stage-dependent use of platinum-based first-line chemotherapies. Nevertheless, 10% of these patients ultimately relapse. Sequential high-dose chemotherapy (HDCT) with autologous stem cell transplantation offers a curative option in such patients. However, the number of HDCT cycles needed remains controversial.
Methods: In this single-center retrospective study, we analyzed the survival rates of 36 consecutive relapsed germ-cell cancer patients treated with three or fewer than three sequential HDCT as salvage treatment between 01/1997 and 12/2013.
Results: 34 of 36 patients had metastases at first diagnosis, with five patients having CNS metastases. Histology was seminoma in ten patients. First-line regimens were BEP (32 pts), VIP (3 pts) or TIP (1 pt), and 35 of 36 patients received three or more cycles. Relapsed patients were treated with carboplatin, etoposide and cyclophosphamide combination chemotherapy until 12/2000 (n=8), or carboplatin and etoposide since 01/2001 (n=28). 21 patients received three sequential HDCT, eight patients hat two HDCT, and seven patients underwent one HDCT. Reasons for not having three HDCT were poor performance status (4 pts.), patient decision (4 pts.), toxicities (3 pts.), early progression (2 pts.), physician decision (1 pt.) and suicide (1 pt). Remission rates were CR2 (18 pts.; 50%), PR2 (8 pts.; 22%); PD2 (6 pts.; 16.7%) and not evaluable in four patients (early death; 11.1%). After a median follow-up of 84 months, 44% of all patients remained in CR2, and overall survival (OS) was 58.3%. OS and PFS at two years were better in patients with three HDCT versus fewer (85% vs 33.3%, *P*=.0034; and 70% vs. 26.7%, *P*=.0044, respectively).
Conclusion: Our data suggest that three sequential HDCT are associated with better OS and PFS than fewer than three HDCT. We currently extend this analysis to all Swiss patients with relapsed germ-cell tumor treated in this time period.

P439 Neutrophil and monocyte CD64 expression provides limited diagnostic value for detection of Graft-versus-host disease or viral infections in patients after allogeneic hematopoietic stem cell transplantation

Federico Simonetta, Amandine Pradier, Stavroula Masouridi-Levrat, Carine Bosshard, Carole Dantin, Cassandra Hogan, Thomas Matthes, Yves Chalandon, Eddy Roosnek
Division of Hematology, Geneva University Hospitals, Geneva, Switzerland

Introduction: CD64 expression by neutrophils and monocytes has been proposed as a diagnostic marker of infection or inflammation. In the present study we evaluated the diagnostic power of CD64 levels for identification of viral infections or Graft versus Host Disease (GvHD) in allogeneic hematopoietic stem cell transplant (HSCT) recipients.
Methods: We performed a prospective study on 295 blood samples obtained at different time points from 80 patients after allogeneic HSCT. We measured CD64 levels on mature CD10-positive neutrophils (nCD64) and on monocytes (mCD64) as well as plasma levels of C-reactive protein (CRP) in HSCT recipients without complications or with viral infections or GvHD. Receiver operating characteristic curve analysis was performed to determine the discriminatory potential of nCD64, mCD64 and CRP for diagnosis of viral infections and GvHD in HSCT recipients.
Results: nCD64 but not mCD64 was significantly up-regulated during early phases after HSCT even in the absence of infectious complications. Levels of nCD64 [MFI: 3.26 (2.07-5.37) vs 2.89 (1.89-4.48), p=0.0079] and mCD64 [MFI: 38.5 (29.7-51.5) vs 32.1 (20.2-52.0), p=0.0078] in patients with GvHD were significantly higher than in patients without but we did not detect significantly higher nCD64 and mCD64 levels in patients with viral infections. Hence, nCD64 and mCD64 expression had only a weak discriminatory power for detection of viral infections or GvHD. nCD64 and mCD64 had an area under the curve (AUC) value of 0.557 and 0.503, respectively, for viral infections and of 0.605 and 0.631 for GvHD. Importantly, nCD64 and mCD64 levels were not more discriminatory than CRP-levels (AUC of 0.570 for viral infections and of 0.629 for GvHD).
Conclusion: nCD64 and mCD64 levels are increased during GvHD but have only a low diagnostic potential for the occurrence of GvHD or viral infections and their use for diagnostic purposes cannot be recommended.

P440 Schedule dependent cytotoxicity of p53 targeted treatment combined with conventional chemotherapy in AML

Katja Seipel[1], Miguel Texeira-Marques[2], Martin Schmid[2], Beatrice U. Mueller[2], Thomas Pabst[1]
[1]Department für Medizinische Onkologie, Inselspital, [2]Department für Klinische Forschung, Universität Bern, Bern, Switzerland

Introduction: Conventional induction chemotherapy induces morphologic complete remission in up to 80% of AML patients, but only 40-50% of patients will ultimately be cured after consolidation treatment. Thus, further improvement of the quality of remission is an urgent need in AML treatment. The master tumor suppressor *p53* is functionally repressed in AML cells by various molecular mechanisms many of which can be specifically targeted. However, the optimal treatment schedule for *p53* targeted compounds and conventional chemotherapy in AML cells is unknown.
Methods: We systematically investigated cytotoxic effects of combined versus sequential application of conventional chemotherapy and various *p53* targeted compounds in a comprehensive series of AML cell lines with or without preserved *p53* function. Conventional chemotherapy comprised the combination of idarubicine and cytarabin, and *p53* targeted compounds included the *MDM2* inhibitor nutlin-3A, the *Exportin* inhibitor leptomycin-B, the *NAE* inhibitor MLN4924, and the *p53* activator APR-246. We assessed cell viability by *in vitro* toxicity assays and *p53* restoration by quantitative RT-PCR and Western blot analysis.
Results: We found that the simultaneous application of conventional chemotherapy together with the *MDM2* inhibitor nutlin-3A exhibited a significant synergistic increase in cytotoxicity and *p53* induction. In contrast, parallel administration of the *Exportin* inhibitor leptomycin-B or the *NAE* inhibitor MLN4924 even antagonized cytotoxic effects of conventional cytotoxic compounds. However, pretreatment with MLN4924 given 24 hours before starting conventional chemotherapy induced a significant synergistic increase in

cytotoxicity and *p53* induction. Finally, simultaneous or sequential administration of the *p53* activator APR-246 together with conventional chemotherapy was not associated with enhanced cytotoxic effects.
Conclusion: Our data identified synergistic antileukemic effects for the simultaneous use of conventional induction chemotherapy together with the *p53* targeting compound nutlin-3A and for the sequential administration of MLN4924 given as pretreatment before chemotherapy. This study highlights the importance of optimized treatment schedules if novel targeted anticancer compounds are combined with standard cytotoxic treatment.

P441 Numerical impairment of nestin$^+$ bone marrow niches in acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia

Michael Medinger[1], Werner Krenger[1], Akos Jakab[1], Christoph Bucher[1], Jakob Passweg[1], Alexandar Tzankov[2]
[1]Hämatologie, [2]Institut für Pathologie, Universitätsspital Basel, Basel, Switzerland

There is increasing evidence suggesting that the perivascular bone marrow stem cell niche and intramedullar neoangiogenesis are involved in GvHD. Tissue-resident nestin$^+$ multipotent stem cells seem to be involved in vessel stabilization and the nestin$^+$ perivascular bone marrow compartment is considered to represent the reticular hematopoietic stem cell niche (HSCN). To study whether GvHD impairs the number (and thus the function) of the nestin$^+$ HSCN, we examined a test cohort of 8 patients with acute myelogenous leukemia (AML), who had undergone allogeneic hematopoietic stem cell transplantation (HSCT). All were in complete remission and had none (n=4) or acute GvHD (aGvHD; n=4). For result confirmation we examined a validation cohort of additional 40 AML patients, of whom 20 had no aGvHD, 9 suffered from aGvHD grade 1 and 11 had clinically relevant (≥ grade 2) aGvHD. We performed immunohistochemical studies of the respective bone marrow biopsies obtained roughly 1 to 4 months after HSCT using antibodies against nestin, CD34 (for bone marrow microvessel density [MVD] determination), pro-collagen 1, and FoxP3. In the test cohort nestin$^+$ HSCN per mm^2 were significantly reduced in patients with aGvHD compared to patients without aGvHD (1.2 ± 0.78 versus 2.6 ± 0.93, p=0.04). In the validation cohort an increased MVD in patients with aGvHD (18.7 ± 5.7 versus 12.7 ± 4.3 vessels/mm^2; p=0.001) was observable, whereas nestin$^+$ HSCN were reduced (1.9 ± 0.99 versus 2.6 ± 0.90 nestin$^+$ HSCN/mm^2, p=0.05) (Table 1).

Table 1. Nestin$^+$ hematopoietic stem cell niches and CD34 microvessel density (MVD) in acute myelogenous leukemia patients 1 to 4 months after allogeneic hematopoietic stem cell transplantation.
Abbreviations: aGvHD = acute graft-versus-host disease; HSCN = hematopoietic stem cell niches

	Test cohort (n=8)		Validation cohort (n=40)			
	no aGvHD	aGvHD	no aGvHD	aGvHD	aGvHD 0-1	GvHD≥2
n	4	4	20	20	29	11
nestin$^+$ HSCN (clusters/mm^2)	2.6 ± 0.93	1.2 ± 0.78	2.6 ± 0.90	1.9 ± 0.99	2.4 ± 0.97	1.8 ± 0.98
P Mann-Whitney U test	0.04		0.05		0.09	
CD34-MVD (vessels/mm^2)	13.1 ± 6.2	18.7 ± 5.9	12.7 ± 4.3	18.7 ± 5.7	14.4 ± 5.9	19.5 ± 4.1
P Mann-Whitney U test	0.004		0.001		0.007	

[Table 1]

Receiver operating curves and Youden's index suggested a potential discriminatory power of nestin$^+$ HSCN quantities for the set-variable "aGvHD" (AUROC=0.68, p=0.05) and the cut-off score best discriminating between patients with and without clinically relevant aGvHD was 2.29 nestin$^+$ HSCN/mm^2. Applying this cut-off score 9/11 patients with clinically relevant aGvHD (≥grade 2) and 13/20 with any GvHD had decreased nestin$^+$ HSCN numbers compared to only 10/29 patients without clinically relevant aGvHD (p=0.007) and 6/20 patients without any GvHD (p=0.028). We found no significant differences regarding FoxP3$^+$ cell and pro-collagen 1$^+$ osteoblast quantities in patients with and without aGvHD. Taken together, our results suggest that increased new vessel formation and numeric drop of nestin$^+$ HSCN are involved in aGvHD.

P442 NK cell functional impairment after allogeneic hematopoietic stem cells transplantation is associated with reduced T-bet and Eomes expression

Federico Simonetta, Amandine Pradier, Carine Bosshard, Stavroula Masouridi-Levrat, Yves Chalandon, Eddy Roosnek
Division of Hematology, Geneva University Hospitals, Geneva, Switzerland

Introduction: NK cells play a major role in protection against tumors and infections. They are the first lymphocyte subset to recover after allogeneic hematopoietic stem cell transplantation (alloHSCT). Impaired NK function after alloHSCT has been reported but underlying mechanisms are ill-defined. Eomesodermin (Eomes) and T-bet, two T-box transcription factors, have been recently reported to regulate maturation and effector functions of NK cells. Their potential impact on NK cell function after alloHSCT are still unknown.
Methods: We analyzed by flow cytometry Median Fluorescence Intensity Ratios (MFIR) of Eomes and T-bet in CD56dim or CD56bright NK cells from 44 healthy controls (HC) and 72 patients undergoing alloHSCT at our center. Ex vivo expression of granzyme B and perforin was analyzed in CD56dim cells. We used non-parametric Mann-Whitney test or Spearman's rank test where appropriate.
Results: T-bet levels were strongly reduced in both CD56bright [MFIR 6.2 (IQR 3.0-9.3)] and CD56dim NK 7.5 (3.2-13.6) cells from HSCT recipients compared with healthy controls [CD56bright 19.0 (14.6-27.2), $p< 0.0001$; CD56dim 21.8 (17.4-31.9), $p< 0.0001$]. Similarly, Eomes was expressed at significantly lower levels in both CD56bright [6.9 (3.3-14.3)] and CD56dim [4.7 (16.6-8.8)] NK cells from HSCT recipients of compared with cells from healthy controls [CD56bright 22.6 (13.5-31.5), $p< 0.0001$; CD56dim 11.2 (6.9-2.5), $p< 0.0001$]. Importantly, we found that acute but not chronic GvHD was associated with significantly reduced levels of T-bet in CD56bright NK cells ($p=0.0386$). Moreover, CMV reactivation was associated with lower levels of Eomes in CD56bright ($p=0.0208$) and CD56dim ($p=0.0129$) NK cells and reduced expression of T-bet in CD56dim NK cells ($p=0.0197$). Perforin expression in NK cells from alloHSCT recipients was lower than in healthy controls. Interestingly, we found a significant correlation between reduced T-bet levels and altered perforin expression ($r=0.2624$, $p=0.0486$).
Conclusion: The expression of the T-box transcription factors Eomes and T-bet is significantly reduced in NK cells after alloHSCT. Moreover, reduction in Eomes and T-bet expression is associated with NK functional impairment. Our results provide a molecular explanation for the reduced NK cell function after alloHSCT previously reported.

P443 Impact of the different approaches of in vivo T-cell depletion on NK cell subsets reconstitution after allogeneic hematopoietic stem cell transplantation

Yordanka Tirefort, Federico Simonetta, Amandine Pradier, Carine Bosshard, Anne-Pascale Grandjean, Yan Beauverd, Stavroula Masouridi-Levrat, Thomas Matthes, Eddy Roosnek, Yves Chalandon
Service d'Hématologie, Hôpitaux Universitaires de Genève, Genève, Switzerland

Introduction: T cell depletion (TCD) is well established for graft-versus-host disease (GVHD) prevention after allogeneic hematopoietic stem cell transplantation (HSCT).Unfortunately,TCD is associated with delayed T-cell reconstitution (T-R) and higher rates of disease recurrence and infection.While all TCD approaches significantly affect T-R after HSCT,little is known about their effect on NK cells,major players in anti-tumoral and anti-infectious immunity after HSCT.We assessed two different TCD approaches employed at our institution,*in vitro* alemtuzumab graft treatment and *in vivo* polyclonal antithymoglobulin (ATG) administration, on NK-R after HSCT.
Patients and methods: We retrospectively analysed 714 blood samples from 123 patients transplanted at our center between 1995 and 2014; 25 patients had partial TCD (pTCD) grafts, consisting of in vitro alemtuzumab,followed on day+1 by add-back donor TCD3+; 37 patients received in vivo ATG; 44 patients had combined ATG and pTCD; 17 patients had no TCD.Linear regression analysis was employed to compare T-cell and NK-R kinetics in patients receiving T-cell replete grafts with patients treated with different TCD protocols.A confirmatory cross-sectional analysis was performed at 1, 6 and 12 months (Mann Whitney test).
Results: As expected,T-R was delayed in patients receiving pTCD grafts ($p< 0.0001$), in vivo ATG

($p< 0.0001$) or both ($p< 0.0001$) compared to non TCD grafts.Importantly,no significant difference was observed in T-R kinetics among all groups of TCD.We found similar NK counts at 1 month after HSCT in recipients of T-cell replete grafts compared to patients receiving pTCD, ATG or combined pTCD/ATG. During the first year after HSCT, NK-R was not affected by either pTCD or ATG alone,while there was a significant expansion of NK in recipients of combined pTCD and ATG when compared with not TCD group ($p=0.0003$).This was confirmed in classical cross-sectional analysis.When NK subsets were analysed, we found similar decline in CD56bright NK in all groups,while there was preferential expansion of the CD56dim NK in combined pTCD/ATG treated patients compared with non TCD grafts.
Conclusion: NK-R was not affected by either pTCD or ATG alone, while combined pTCD and ATG was associated with rapid and sustained NK expansion in the first year after HSCT.These data extend our knowledge about the effects of TCD on immune-reconstitution after HSCT.Further studies are needed to evaluate the clinical impact of such results.

P444 PU.1-regulated ATG16L2 functions in AML differentiation and autophagy

Jing Jin[1,2], Mario P. Tschan[1,2]
[1]Experimental Pathology, TP2, Institute of Pathology, University of Bern, [2]Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

Introduction: Acute myeloid leukemia (AML) is characterized by an accumulation of non-differentiated myeloid progenitors. The transcription factor PU.1 is a key organizer of myeloid development and its low expression contributes to the pathogenesis of AML. Myeloid differentiation also depends on autophagy, a cellular recycling machinery characterized by the formation of autophagosomes. We previously reported that expression levels of autophagy-related (ATG) genes are frequently downregulated in primary AML blast cells and that low ATG mRNA levels are associated with an immature myeloid phenotype. Interestingly, a recent publication stated that ATG16L2 does not function in starvation-induced canonical autophagy.
Methods: ATG16L2 mRNA expression was quantified by qPCR in primary AML patient samples taken at diagnosis. AML cell lines (NB4, HL60, HT93) were differentiated using all-*trans* retinoic acid (ATRA) and neutrophil differentiation was assessed by CD11b FACS and CEBPE mRNA expression. PU.1 and ATG16L2 knockdown cell lines were generated using lentivirally delivered shRNAs. Autophagic flux was determined by LC3B western blotting and long-lived protein degradation assays. Chromatin immunoprecipitation (ChIP) to test binding of PU.1 to the ATG16L2 promoter.
Results: ATG16L2 is one of the most highly repressed genes in primary AML patients of all subtypes analyzed as compared to the expression in healthy neutrophils. In line with these findings, ATRA-mediated neutrophil differentiation of three different AML cell lines results in a significant induction of ATG16L2 message levels. NB4 cells depleted of ATG16L2 displayed significantly attenuated neutrophil differentiation as well as myeloid autophagy. Induction of ATG16L2 during this process is PU.1-dependent and we found binding of PU.1 to the ATG16L2 promoter region. Moreover, ATG16L2 expression was partially restored when AML cells were treated with the demethylating agent 5-aza-2 deoxycytidine.
Conclusion: Our studies clearly show a critical function for ATG16L2 in ATRA-induced neutrophil differentiation and autophagy. This is in contrast to starvation-induced autophagy, which is not dependent on ATG16L2 and further points to a particular type of autophagy during AML differentiation. Low ATG16L2 levels in primary AML patient samples can be attributed to low expression of its positive transcriptional regulator PU.1 as well as to epigenetic silencing.

P445 Depletion of the glycolytic enzyme PKM2 allows neutrophil differentiation of ATRA-resistant APL cells

Julia Parts[1,2], Mario P. Tschan[1,2]
[1]Experimental Pathology, TP2, Institute of Pathology, University of Bern, [2]Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

Introduction: A majority of cancer cells rely on metabolic intermediates from aerobic glycolysis to satisfy their increased demand for biosynthesis (Warburg effect). To this end, tumor cells frequently express the M2 isoform of pyruvate kinase (PKM2), which catalyzes the last step within glycolysis. Interestingly, murine normal hematopoietic and leukemic cells preferentially express PKM2 and this enzyme is needed for leukemia progression in mice. In addition to its metabolic function, nuclear PKM2 is involved in gene regulation, e.g. activation of cyclin D and C-myc via β-catenin. We now asked if PKM2 plays a role in cellular differentiation of APL cells.
Methods: PKM2 mRNA expression levels were measured by qPCR in primary AML patient samples, healthy neutrophils and in APL cell lines. NB4 APL PKM2 knockdown cells were generated using lentivirus encoding shRNA targeting PKM2. PKM2 knockdown efficiency and nuclear localization upon cell fractioning were determined by Western blotting. Cell differentiation and functionality was assessed by G-CSF-R mRNA levels, CD11b surface marker expression and nitro blue-tetrazolium reduction.
Results: PKM2 is significantly downregulated in primary AML patient samples as compared to healthy granulocytes. Accordingly, PKM2 mRNA (10-15-fold) and protein levels were significantly induced upon ATRA-mediated neutrophil differentiation of parental but not ATRA-resistant NB4-R1/R2 APL cells. Increased expression of PKM2 was also seen during neutrophil differentiation of non-APL HL60 cells. Surprisingly, knocking down PKM2 in NB4 cells did not attenuate neutrophil differentiation. In contrast, depleting PKM2 in ATRA-resistant NB4-R1/R2 cells led to significantly enhanced neutrophil differentiation. Importantly, knocking down PKM2 caused minor, but significant neutrophil differentiation in NB4R1/R2 cells without ATRA treatment. Lastly, we found nuclear PKM2 expression in NB4-R2 cells and depleting PKM2 in these cells resulted in decreased c-Myc expression. Together, knocking down PKM2 partially rescues neutrophil differentiation of ATRA-resistant NB4 cells.
Conclusions: Targeting PKM2 in differentiation impaired APL cells may resensitize these cells to retinoic acids.

P446 Effects of all trans retinoic acid (ATRA) and arsenic trioxide (ATO) on tissue factor (TF) expression by cultured APL cells. Potential contribution of tumor necrosis factor alpha (TNF and interleukin-1beta (IL1b)

Sylvie Geindre[1], Anne-Sophie Rivier-Cordey[1], Olga Tsopra[2], Lecompte Thomas[2], Egbert Kruithof[1]
[1]Service d'Angiologie et d'Hémostase, Université de Genève/Faculté de Médecine, [2]Hématologie, Hôpitaux Universitaires de Genève, Genève, Switzerland

Background: Acute promyelocytic leukemia (APL) is a characterized by disseminated intravascular coagulation and severe hemorrhagic complications, caused in part by the high expression of tissue factor (TF) on APL cells and microparticles. APL cells also produce TNF and IL1b, inflammatory cytokines (CK) known to increase TF expression in monocytes and endothelial cells and potentially acting in an autocrine way on APL cells. ATRA and ATO are clinically used for the treatment of APL, but their impact on TF and CK production is only partially characterized.
Aims and methods: To study in NB4 APL cells: - the effect of ATRA (1 μM) or ATO (0.5 μM) on mRNA and protein of TF, TNF and IL1b; - the contribution of TNF and IL1b to TF production and activity using the inhibitors adalimumab and anakinra, respectively; and - the effect on TF expression of inhibitors of the inflammatory signaling intermediates, NFkB, p38 and jun kinase.
Results:
Effect of treatments on mRNA levels

	TF	TNF	IL1b
ATRA*	-95%	-86%	+300%
ATO*	-80%	-60%	+280%
Adalimumab	-33%	ND	ND
Anakinra	-21%	ND	ND
NFkB inhibition	-65%	-78%	no effect
P38 inhibition	-38%	+500%	+2500%
jun kinase inhibition	no effect	no effect	-80%

[Mean of 4 experiments at 24h]

*The effect of ATRA on TF (max after 1h) precedes its effect on TNF (max after 16h).
** The effect of ATO on TF (max after 6h) parallels its effect on TNF (max after 6h).
Treatment with ATRA or ATO reduced cell and microparticle associated TF antigen and TF activity by more than 75 and 50%, respectively.
In addition, with the NFkB inhibitor BAY11-7085 a marked reduction in cell survival was observed within hours.
Discussion: Our results suggest that TNF and IL1b contribute partially to TF expression by APL cells. However, ATRA reduces TF mRNA before TNF mRNA and inhibition of TNF or IL1b only partially reduces TF mRNA. This implies that TF production does not depend only on these CK. The potentially deleterious effects of the increase in IL1b induced by ATRA must be taken into account. Inhibitors of p38 partially reduce TF RNA, even though TNF and IL1b mRNA are strongly increased, while NFkB inhibition reduces TF and TNF expression.
None of the approaches to reduces CK activity or CK signaling reproduce the effect of ATRA. This implies that the effect of ATRA on TF is not only mediated by effects of ATRA on inflammatory CK. Of note NFkB inhibition strongly affects cell survival, which would offer a potential adjunct therapy of APL.

P447 Phenotypic assays using zebrafish hematopoesis models for elucidation of hematopoietic toxicity

Anna Lenard[1], Claudia McGinnis[2], Claudia Lengerke[1]
[1]Department of Biomedicine, Universitätsspital Basel, [2]Roche Innovation Center Basel, Basel, Switzerland

Hematologic toxicity is one of the most common side effects encountered in preclinical safety testing of new drug candidates. The consequences of direct or indirect damage to blood cells and their precursors can be potentially life threatening, and hence, hematotoxicity can lead to the termination of a promising drug candidate.
Currently performed hematotoxicity assays rely on *in vitro* models with cell viability read-outs and laborious mammalian animal models. However, this approach only allows a limited assessment and, for example, does not capture effects on full maturation and functionality of blood cells. Here, we propose zebrafish as an alternative animal model that captures the full range of hematopoietic lineages and maturation stages in an *in vivo* setting while at the same time providing several advantages. Their small size, the ease of handling and culture, and the transparent nature of the larval stages, make zebrafish an accessible, *in vivo* imaging-friendly vertebrate model. We use several transgenic reporter lines that express fluorescent proteins under lineage-specific promoters and can be used for imaging and chemical screens. Using high-content *in vivo* live cell imaging we analyze defined hematopoietic lineages with regards to cell numbers, distribution and functional activity. Additionally, fluorescent cell numbers are measured by flow cytometry.
Doxorubicin and Vinorelbine were evaluated as first compounds to test the system. Dose titration experiments were performed *in vivo* with both drugs and concentrations that did not grossly impair embryonic development were identified. Preliminary results indicate reduction of *gata1* red cell progenitors following treatment with Vinorelbine. Further data, including functional data on macrophage activity in an

injury model are currently collected.
These results will serve to validate the utility and sensitivity of this new model system, which eventually can contribute to preclinical safety testing of new therapeutic compounds.

P448 High BAFF level but low APRIL levels mark the acute acquired Thrombotic Thrombocytopenic Purpura bout

Monica Monica Schaller, Tabea Schmocker, Irmela Sulzer, Magdalena Skowronska, Johanna Anna Kremer Hovinga
Hematology, Central Laboratory of Hematology and Clinical Research, University Hospital and University of Bern, Inselspital, Bern, Switzerland

Aim: What causes the brake down of tolerance towards ADAMTS13 in acquired Thrombotic Thrombocytopenic Purpura (aTTP) is still not resolved. Increasing evidence points at a dysregulated production of tumor necrosis factor (TNF) family members BAFF and APRIL supporting autoreactive B-cell development, survival and maturation in autoimmunity. We investigated if plasma levels of BAFF/APRIL correlate with clinical manifestations of aTTP.
Method: From 17 aTTP patients, 3/17 relapsing, suffering from a severe ADAMTS13 deficiency with positive inhibitors as diagnosed at our Center (2005-2014), a total of 144 follow-up samples were analysed for BAFF/ARPIL levels in comparison to a healthy control group (n=22) using commercial immunoassay techniques Quantikine ELISA Kit (R&D Systems, Abingdon, UK, BAFF) and TNFSF13 (Abnova, Taiwan, APRIL).
Results: All aTTP patients showed slightly elevated mean BAFF levels [851 pg/ml (range 101-4000), P=0.329] but equal mean APRIL levels [7.6 ng/ml (range 1.2-100)] when compared to the control group [BAFF: 625 (range 490-862) or APRIL: 5.4 ng/ml (range 1.3-100)]. No correlation between BAFF and APRIL levels was observed. Remarkably at onset of 3/3 relapsing aTTP patients, higher mean BAFF [864 pg/ml], but lower APRIL levels [5.1 ng/ml] were observed compared to 8/14 non-relapsing patients with mean BAFF levels [743 pg/ml (range 532-1220) or to 9/14 patients with mean APRIL levels [2.9 ng/ml (range 0.6-4.8). In remission BAFF levels decreased while APRIL levels increased for all aTTP patients but ~ 100 days prior (BAFF) or ~ 60 days (APRIL) a next bout, levels increased (BAFF) or decreased (APRIL) at least to or above onset levels. Rituximab (2/17) or splenectomy (1/17) lead to increased BAFF, but decreased APRIL levels.
Conclusions: High BAFF and low APRIL levels mark the acute phase of aTTP hinting at a potential beneficiary effect of anti-BAFF antibody treatment for aTTP patients suffering from a relapsing disease course.

P449 The role of *trps1* transcription factor in zebrafish hematopoietic development

Elisa Alghisi[1], Martina Konantz[1], Claudia Lengerke[1,2]
[1]Department of Biomedicine, [2]Abteilung für Hämatologie, Universitätsspital Basel, Basel, Switzerland

The *EVI1* (ecotropic viral integration site 1) gene is a zinc finger transcriptional regulator that is expressed in hematopoietic stem cells and regulates their emergence during development via up-regulation of the *NOTCH* pathway in the aorta-gonado-mesonephros (AGM) region of the dorsal aorta (Konantz et al, personal communication). However, the precise molecular mechanism of EVI1-mediated *NOTCH*-induction is unclear. Next to its role in development, *EVI1* is a well-known oncogene in acute myeloid leukemia where its overexpression indicates particularly poor prognosis. Recent analyses of expression databases of *MLL*-rearranged acute myeloid leukemia revealed high concomitant expression of the transcription factor *TRPS1*. To our knowledge, there are currently no published data on the role of *TRPS1* in hematopoiesis.
The trichorhinophalangeal syndrome 1 (*TRPS1*) is a *GATA* family transcriptional factor known for its role in chondrocyte and perichondrium development. Nonsense mutations in this gene are associated with an autosomal dominant multisystem disorder characterized by facial abnormalities, brachydactyly and skeletal

dysplasia. Different reports suggest its involvement in oncogenesis: *TRPS1* is highly overexpressed in colon cancer, and in breast cancer induces epithelial-to-mesenchymal transition through the *miR-221/222* pathway and angiogenesis through activation of its direct target gene *VEGF*.
Here we take advantage of the zebrafish model to study the role of the zebrafish homologue trps1 during zebrafish hematopoietic development and explore potential interactions with evi1. Especially we would like to investigate whether *trps1* is a downstream-target of *evi1* mediating via *vegf* its inductive effect on the *notch* pathway. Preliminary data show that indeed knockdown of *trps1* with morpholinos reduced emerging hematopoietic stem cells as identified by *cmyb/runx1* expression *in situ* hybridization in AGM region and also *rag1* positive lymphoid cells in the thymus indicating a functional role in definitive hematopoiesis. Co-injection of *evi1* mRNA was not able to rescue *runx1* expression in *trps1* morphants, suggesting that indeed *trps1* may act as an *evi1* downstream target. Rescue experiments of *evi1* morphants with *trps1* mRNA further exploring this hypothesis are underway.
Taken together, our preliminary data indicates an unsuspected role of *trps1* in hematopoiesis and suggest possible molecular correlations between *evi1* and *trps1* during blood stem cell development.

P450 Increased fibrinogen levels at diagnosis are associated with adverse outcome in patients with acute myeloid leukemia

Alexander Heini[1], Martin D. Berger[1], Anne Angelillo-Scherrer[2], Thomas Pabst[1]
[1]Department für Medizinische Onkologie, [2]Department für Hämatologie, Inselspital, Bern, Switzerland

Background: Increased plasma fibrinogen levels were reported to be associated with shortened overall survival in some solid tumors types. In patients with acute promyelocytic leukemia (APL), low plasma fibrinogen levels are often seen at diagnosis. However, the prognostic significance of fibrinogen levels *per se* in AML patients has not been reported so far.
Methods: In this single-center study, we retrospectively investigated the survival rates of 467 consecutive AML patients with respect to their fibrinogen levels at diagnosis.
Results: We identified 437 AML patients with available fibrinogen plasma levels at diagnosis. 306 patients underwent intensive treatment and 131 patients received best supportive care. The 306 AML patients with intensive treatment were dichotomized between having normal (< 4.2mg/l) or increased fibrinogen levels (≥4.2mg/l). The clinical characteristics at diagnosis between the two groups were equally balanced. However, patients in the normal fibrinogen group had more frequently APL (12.7% vs 1.1%). Rates of complete remission (65.9% vs 66.3%) and early death rates at 30 days (11.9% vs 12.6%) and 100 days (23.2% vs 25.1%) were not different. Also, admission rates to the intensive care unit were similar (32.1% vs 34.9%). However, overall survival (OS) was significantly better in the normal fibrinogen group (39.2 vs 24.5 months) as well as progression free survival (PFS; 36.3 vs 22.6 months).
Conclusion: This is the first study evaluating the prognostic significance of plasma fibrinogen levels at diagnosis of AML. Our results suggest that elevated fibrinogen levels are associated with unfavorable OS and PFS in AML, but not with increased mortality during induction treatment.

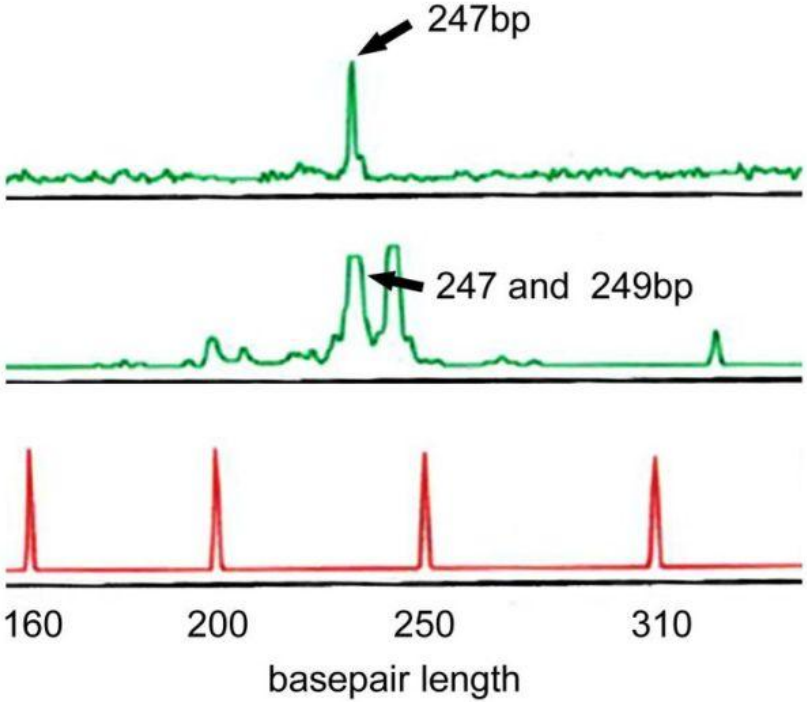
Gastgesellschaft: Poster SGH

Société conviée: Session de poster SSH

P451 Destructive myocarditis induced by preclinical T-PLL

Christian Arno Arranto[1], Otmar Pfister[2], Alexandar Tzankov[3], Jakob Passweg[1], Claudia Lengerke[1]
[1]Hämatologie, [2]Kardiologie, [3]Pathologie, Universitätsspital Basel, Basel, Switzerland

A 68 year old male patient presented with rapid progression of dyspnea after two episodes of acute bronchitis within 3 months which were treated in an ambulatory setting. The transthoracic echocardiography showed a cardiomegaly. The cardiac-MRI demonstrated a septal and basal intramyocardial late-enhancement compatible with myocarditis. Coronary angiography excluded a relevant stenosis and the ventriculography showed a dilated left ventricle with severe reduced function (LVEF 20-25%). The myocardial biopsy showed a multifocal, partially fresh lymphocytic myocarditis. Nested-PCR for several viruses were negative. The patient was treated with a beta-blocker, angiotensin-receptor blocker, diuretics, amiodarone and a statin. Four years later the patient was upgraded to a CRT-ICD due to symptomatic slowly further decline of the left ventricular function to 15% with severe dilation and mitral regurgitation. The patient was referred to the hematologist due to a new lymphocytosis with thrombopenia and normal hemoglobin. A computer tomography showed no lymphadenopathy or splenomegaly. Flow cytometric analysis from the blood and bone marrow demonstrated a CD4+/CD8+ double positive T-lymphocytosis and with a biclonal T-cell receptor rearrangement. The diagnosis of a T-prolymphocytic leukemia (T-PLL) was made. Six months later the patient received a left-ventricular assist device due to further progression of his heart failure. The myocardial biopsy showed lymphocytic infiltration of the T-PLL which was proven by the same biclonal T-cell receptor rearrangement as in the bone marrow. A re-analysis of the myocardial biopsy at initial diagnosis four years earlier demonstrated the presence of a single T-cell rearrangement (Figure 1: upper green line) which matched with one of the current T-cell gene rearrangement products (Figure 1: lower green line).
T-PLL is a rare leukemia with a median age of 65 years. In 60% of patients the cells are CD4+, CD8- and in 25% they coexpress CD4 and CD8 as in the present case, a feature almost unique to T-PLL. The median survival is usually less than one year but cases of more chronic course have been reported. Cardiac leukemic infiltration is a known phenomenon in patients with acute leukemia.
To our knowledge this is the first case, in which cardiac infiltration by T-PLL cell is demonstrated over a long period of time and lead potentially to severe heart failure.



[Figure 1]

P452 CML therapy in the 3rd generation TKI era: spoiled for choice

Mathilde Gavillet, Jasmine Nötzli, Claire Abbal, Olivier Spertini
Service d'Hématologie, CHUV, Université de Lausanne, Lausanne, Switzerland

Introduction: Five BCR-ABL tyrosine kinase inhibitors (TKIs): imatinib, nilotinib, dasatinib, bosutinib and ponatinib, are currently approved for the treatment of chronic myeloid leukemia (CML). Landmark studies report drug treatment discontinuation in 20-25% of study subjects, 5 to 13% due to drug adverse effects.
Method: In order to assess the frequency of drug treatment discontinuation and its causes in a real-life setting, we retrospectively collected data about all consecutive CML cases treated in our center between 2000 and 2014. We analyzed the treatment response (according to ELN guidelines), the number of treatment regimens received and graded drug adverse effects (using the NCI common toxicity criteria).
Results: Thirty patients with CML in chronic phase were identified (16 males, 14 females). Mean age was 57.6 years (range 25 to 84) and median follow up of 70.3 months. Thirteen patients (43.3%) were still under the first line therapy (12 Imatinib; 1 Nilotinib). A total of 39 drug changes were recorded: 16 (41.1%) were motivated by suboptimal or loss of response. BCR-ABL kinase domain analysis revealed 3 acquired mutations, which subsequently guided the next drug choice. 23 drug change (58.9%) were caused by drug intolerance or adverse effects (6 grade 1, 3 grade 3, 11 grade 3 and 2 grade 4). One patient underwent allogenic stem cell transplant after failure of 4 TKIs due to severe drug toxicity attributed to a class effect. 4 loss of response without identifiable mutation (10.2% of drug changes) were retrospectively attributable to poor treatment adherence caused by drug side effects (all grade 1-2). In the subgroup with grade 1-2 drug side effect, change to a second generation TKI did not provide symptoms relief. Patient's treatment adherence and therapeutic efficiency was obtained with the initial drug plus symptomatic treatment of adverse effects. In our center, adhesion to treatment has also considerably been increased by a drug compliance program in collaboration with our Pharmacy Department, as previously reported.
Conclusion: While numerous potent drugs are available to treat CML, drug tolerance and patient's symptoms remain critical for compliance and efficiency of therapy. These aspects, likely underestimated in large pioneering studies, should be actively assessed using international guidelines and addressed by the physician in charge in order to provide more efficient care.

P453 Opportunity and need for a controlled therapy cessation study in Switzerland

Jasmine Nötzli, Mathilde Gavillet, Claire Abbal, Olivier Spertini Service d'Hématologie, CHUV, Université de Lausanne, Lausanne, Switzerland

Introduction: Since the advent of TKI-based treatments, most patients with chronic myeloid leukemia (CML) achieve a profound and sustained molecular response. For a selection of patients with a deep, stable, long-lasting molecular response, treatment discontinuation is currently the subject of numerous investigational studies with promising results.
Method: In order to assess the number of potential drug cessation candidates in a real-life setting, we retrospectively collected data about all consecutive CML cases treated in our center between 1.1.2000 and 31.12.2014. We analyzed the treatment response (MMR: ≤0.1% BCR-ABL^{IS} and MR4: ≤0.01% BCR-ABL^{IS}) and duration.
Results: Thirty patients with CML in chronic phase were identified (16 males, 14 females). Mean age was 57.6 years old (range 25 to 84) and the median follow up 70.3 months. Twenty three patients (76%) obtained major molecular response after a median of 23.1 months of therapy (13 imatinib, 2 dasatinib, 7 nilotinib, 1 ponatinib) and 22 achieved MR4. This response was sustained for at least 24 months in 18 (60%) and 15 (50%) patients, respectively, thus corresponding to the minimal requirements of the drug discontinuation studies.
Conclusion: The literature data show that about 40% of patients had persistent molecular response 12 months after drug discontinuation. Our data highlight the possibility to open a similar clinical trial even in smaller centers, which would offer considerable comfort and cost advantages to our patient collective.

P454 Hemopagocytic syndrome as a differential diagnosis of fever of unknown origin: a case report

Nebal Abu Hussein[1], Lara Böhne[1], Jakob Passweg[2], Stefan Vogt[1], Susanne Christen[1]
[1]Medizin, Regional Spital Rheinfelden, Gesundheitszentrum Fricktal, Rheinfelden, [2]Hematology, Universitätsspital Basel, Basel, Switzerland

Introduction: Hemophagocytic syndrome (HLH) is disease characterized by fever, splenomegaly, jaundice, and the pathologic finding of hemophagocytosis in bone marrow and other tissues. It is usually associated with malignant, genetic, or autoimmune diseases but is also prominently linked with Epstein-Barr (EBV) virus infection.
Case report: 53 years old patient was admitted to the regional hospital Rheinfelden due to remitting fever rising up to 40 degrees C with Muscle pain mostly in the afternoon since 2 weeks. The clinical examination shows except for splenomegaly an fiver 39°C no pathological findings. Serology shows elevated C-reactive protein (130 mg/l) and elevated lever serology. Multiple blood and urine cultures, serology (Hep A-C, EBV, HIV CMV Q-Fiver) and autoimmune serology and transesophageal echocardiography remained without clinical focus. CT-scan of lung and abdomen revealed splenic lesions, splenomegaly and multiple mediastinal lymph nodes. In Bone marrow biopsy we could rollout multiple myeloma or any malignity but the samples show high level of Ferritin, which suggested hemophagozytosis. The PET-CT shows high activity in multiple mediastinal lymph nodes. The Lymph node biopsy in the university Hospital of Basel confirmed HLH. The patients received steroids according to the HLH2004 protocol.
After 3 cycles of treatment the patient has been readmitted due to fiver 41°C and upper abdominal pain. The serology showed elevated CRP and aplasia. The serial Blood culture and CMV in PCR were negative. This finding suggested aggravation of the disease. Therefor a splenectomy was performed. The chemotherapy was resumed 2 weeks after the operation; the patient tolerated the treatment without complication until today.
Conclusion: HLH in adults is a disorder about which a lot remains to be known; prognosis in adults is poor. HLH in adults is mostly secondary to a trigger, and identification and treatment of the primary etiology is essential for a possible cure. Early diagnosis remains the key to better prognosis. Additional research is required for this Syndrome.

P455 Flow cytometry detection of phosphoproteins and their signalling pathways in acute leukemias

Mathieu Hauwel, Riccardo Favale, Thomas Matthes
Medecine Génétique et de Laboratoires, Hôpitaux Universitaires de Genève, Genève, Switzerland

Flow cytometry profiling of intracellular signalling pathways, including phosphorylation cascades, is a novative approach for both diagnosis of hematological malignancies and patient stratification. It also provides a way to follow, at the cellular level, a new promising class of therapeutic agents: small inhibitors. Whereas detection of surface markers is relatively straightforward, intracytoplasmic or nuclear antigen detection requires sometime a tedious optimisation phase. In the context of clinical diagnosis, establishing SOP is absolutely essential to minimise inter-operator variability. We investigated several staining methods, all routinely applicable, for the characterization of intracellular signalling in acute leukemia patients.

P456 Accelerating the yellow to red bone marrow transition

Vasco Campos[1], Benjamin Rappaz[2], Josefine Tratwal[1], Yannick Yersin[1], Gennady Nikitin[3], Sylke Höhnel[3], Nathalie Brandenberg[3], Matthias Lutolf[3], Gerardo Turcatti[2], Olaia Naveiras[1,4]
[1]Laboratory of Regenerative Hematopoiesis (GR-NAVEIRAS), [2]Biomolecular Screening Facility (BSF), [3]Laboratory of Stem Cell Bioengineering (LSCB), EPFL, [4]Hematology Service, Department of Oncology, CHUV, Lausanne, Switzerland

Worldwide, more than 50.000 bone marrow transplantations are performed annually, although the mortality rate still is close to 50% within the first three years after allogeneic transplantation. Forty percent of these fatalities relate to the patients' severe immune compromise during the post-ablation period, before the graft has fully reconstituted the hematopoietic system. Reducing the time of engraftment is therefore critical to increasing the chance of survival in these patients.
Preventing adipocyte formation, the most abundant cell type in the human bone marrow, in the post-transplant period has been demonstrated to accelerate hematopoietic stem cell (HSC) engraftment and subsequent hematopoietic recovery in mice. We are interested in understanding the kinetics and molecular mechanisms of the highly plastic transition between yellow (adipocytic) and red (hematopoietic) bone marrow.
Bone marrow adipocyte formation was measured in vivo after HSC transplantation and correlated with the kinetics of hematopoietic recovery. After HSC transplantation adipocytes infiltrate the bone marrow reaching maximum expansion after 10 to 15 days. Bone marrow hematopoiesis is recovered after around 25 days, which is consistent with the exit of severe neutro- and thrombocytopenia on day 30 and 35, respectively, and recovery of pre-transplant cell blood counts by day 45.
In order to uncover molecular mediators of the yellow to red transition, we have developed a high-throughput 2D in vitro Mesenchymal Stromal Cell (MSC) culture system. Using Digital Holographic Microscopy we can quantify adipocytic differentiation based on real-time lipid accumulation and screen the Prestwick library of FDA-approved drugs and natural compounds provided by the Biomolecular Screening Facility (EPFL) for inhibitors of adipogenesis. Enhancement of hematopoiesis by these anti-adipogenic candidates is then tested via a novel 3D in vitro HSC/MSC co-culture system using the bone marrow-derived line OP9 and primary murine hematopoietic stem and progenitor cells simultaneously.
All current clinical approaches to enhance hematopoiesis target the HSC itself. Here we propose targeting bone marrow adipogenesis as an alternative strategy to accelerate the yellow to red bone marrow transition thereby improving post transplant survival.

P457 Mapping bone-marrow adipogenesis in homeostasis and aplasia

Josefine Tratwal[1], Chiheb Boussema[1], Olivier Burri[2], Olaia Naveiras[1,3]
[1]Laboratory of Regenerative Hematopoiesis (GR-NAVEIRAS), [2]Bioimaging and Optics Core Facility (PTBIOP), École Polytechnique Fédérale de Lausanne (EPFL), [3]Hematology Service, Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Adipocytes are the most frequent cell type in the adult human bone marrow (BM). Their formation occurs at the expense of the differentiation of preadipocytes and mesenchymal stem progenitors cells (MSPCs) that have been shown key to hematopoietic stem cell (HSC) support. Different subsets of such MSPCs have been described, including human CD146+ cells, and mouse Nestin+, Sca1+ ALCAM-, LeptinR+ cells. The hematopoietic (red) and adipocytic (yellow) marrow are heterogeneously distributed within the BM depending on skeletal location and physiological conditions. A transition of red to yellow marrow occurs with aging, and in juvenile development when distal parts of the skeleton become fully adipocytic during growth as described by Neumann's law. BM aplasia, whether secondary to chemotherapy or inherited BM failure syndromes, is also systematically accompanied by adipocytic infiltration of the marrow. Intriguingly, BM adipocytes accumulate different lipids than subcutaneous adipocytes, and they have features of brown fat-like tissue, compatible with electron microscopy descriptions of multivacuolar adipocytes within the marrow.
Given the inhibitory role of adipocytes in hematopoiesis, we are interested in characterizing the transition from red to yellow marrow in the context of ageing, gender and BM aplasia. To this end, we have developed a semi-automated imaging analysis tool for quantification of BM adipocytes and hematopoietic cells in histological sections. Morphometric analyses are compared with micro-computerized tomography and magnetic resonance imaging in mice as a prospective non-invasive technique to survey whole skeleton BM adipogenesis. HSCs, MSPCs, and their progenitors are characterized by flow cytometry and gene expression analysis in different skeletal locations, while mapping the MSPC progenitors within the white to brown fat axis. To test the efficiency of red and yellow marrow components in recruiting BM-forming units, various

methods of ossicle formation and heterotopic BM adipogenesis are applied. Correlation of findings in mouse to human will be done by analysis of surgical debris from various skeletal locations and by retrospective analysis of human BM adiposity to time to engraftment in recipients.

P458 Methodological shortcomings and design-related bias in studies investigating diagnostic tests for venous thromboembolic diseases - literature survey

Michael Nagler[1,2], Patrick M. Bossuyt[3], Hugo ten Cate[2], Walter A. Wuillemin[4,5], Livia Faes[6], Lucas M. Bachmann[6]
[1]Abteilung Hämatologie und Hämatologisches Zentrallabor, Luzerner Kantonsspital, Luzern, Switzerland, [2]Laboratory of Clinical Thrombosis and Haemostasis, and Cardiovascular Research Institute, Maastricht University Medical Center, Maastricht, [3]Department of Clinical Epidemiology, Biostatistics & Bioinformatics, Academic Medical Center - University of Amsterdam, Amsterdam, The Netherlands, [4]Division of Haematology and Central Haematology Laboratory, Luzerner Kantonsspital, Luzern, [5]University of Bern, Berne, [6]Medignition Inc., Zurich, Switzerland

Background: Relying on suboptimal methods for evaluating diagnostic tests can generate imprecise and biased results and lead to unwarranted optimism about their performance. It is unknown whether this also holds for diagnostic tests for venous thromboembolic diseases.
Methods: We searched Medline and Embase for systematic reviews of diagnostic accuracy studies for five target conditions. Two-by-two tables and the results of the reviews' quality assessment were extracted in duplicate for each primary study included in these reviews. We scored the risk of bias using QUADAS-2 instrument. In a meta-analysis we comparing the summary estimates of the diagnostic odds ratio from studies unlikely to be biased with those from studies likely to be biased.
Results: Eleven systematic reviews summarizing 140 primary studies in 31,046 patients were included. Median sample size was 103 (IQR 50-202); the median number of patients with the target condition was 31 (15-46) versus 68 without (27-152). Adequate quality assessment tools were used in 5 systematic reviews only (46%). Among the 37 primary studies with QUADAS-2 score available, the risk of bias was estimated to be low for all items in five only (14%). Studies unlikely to be biased on all items reported lower DOR (-13.56 (95% CI -46.94 to 19.83); p=0.415).
Conclusions: Diagnostic accuracy in studies on venous thromboembolic diseases are unlikely to report precise point estimates of test performance and are often likely to be biased according to QUADAS-2. Established guidelines to design and report diagnostic tests should be more systematically adopted.

P459 Issue in RBC transfusion: a case of acute and severe post-transfusion hemolysis

Stefano Barelli[1,2], Elena Bianchi[2], Nathalie Imobersteg[1], Sofia Lejon-Crottet[1], Jean-Daniel Tissot[1], Giorgia Canellini[1]
[1]Transfusion Interrégionale CRS, Epalinges - Berne, [2]Service et Laboratoire Central d'Hématologie - CHUV, Lausanne, Switzerland

Introduction: Herein we describe a 54 years old woman with severe and repeated episodes of intravascular hemolysis after transfusion. No causative alloantibodies was detectable despite extensive serological investigations. Blood group genotyping indicated a possible anti-Jk^b (anti-JK2).
Case description: The patient suffering from congenital defects was admitted for colon and vesical corrective surgery during which she received two red blood cell (RBC) units. Due to an urosepsis, an antibiotic therapy was introduced. A progressive anemia developed over the next two weeks and a RBC unit was transfused. Shortly after the transfusion, the patient presented high fever, shivers, signs of shock and passed dark urine. This was not reported since other origins were raised by the clinicians. The hemoglobin (Hb) level fell promptly within 24 hours and imposed the transfusion of two more RBC units which triggered a similar acute reaction with biological signs of intravascular hemolysis and no Hb improvement. Serologic

tests (DAT, antibody screening, elution and cross-match) did not reveal any blood group alloantibodies, except a weak anti-E (anti-RH3) that could not be incriminated, as all the RBC units were RH3 negative. G-6-PD deficiency and paroxystic nocturnal hemoglobinuria were excluded. The decrease of the Hb level below 50 g/l brought to another transfusion. Despite premedication with corticosteroids and a RBC product with reduced plasma volume, intravascular hemolysis occurred early. Consequently, all transfusions were stopped and alternative treatments (immunoglobulin, erythropoietin) were begun. Finally, the anemia recovered and the patient was discharged without long-term complications. As patient's RBC phenotype could not be retrospectively interpreted, a blood group genotyping was performed. Comparing the patient genotype and the phenotype/genotype of the RBC donors, an undetectable anti-JK2 was suspected to be involved in these hemolytic reactions.

Discussion: This case highlights several transfusion medicine rules:

1) delay of announcement: a post-transfusion reaction always needs to be reported to the blood bank,
2) anti-JK2: frequently very difficult to detect and classically associated with severe hemolysis after incompatible blood transfusion,
3) alternative to transfusion: optimisation of hematopoiesis remains the cornerstone of anemia treatment
4) RBC genotyping: this method enables determination of patients RBC antigens even after transfusion.

Gastgesellschaft: SGKPT Poster Presentation Session

Société conviée: SSPTC Poster Presentation Session

P460 Pregnancy outcome following maternal exposure to pregabalin: a reason for concern? A collaborative ENTIS and Motherisk study

Ursula Winterfeld[1], Paul Merlob[2], David Baud[3], Valentin Rousson[4], Alice Panchaud[1], Laura E. Rothuizen[1], Nathalie Bernard[5], Thierry Vial[5], Laura M. Yates[6], Alessandra Pistelli[7], Maria Ellfolk[8], Georgios Eleftheriou[9], Loes C. de Vries[10,11], Pina Bozzo[12], Annie-Pierre Jonville-Bera[13], Mine Kadioglu[14], Jérôme Biollaz[1], Thierry Buclin[1]

[1]STIS and Division of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [2]BELTIS Rabin Medical Center and Sackler School of Medicine, University of Tel Aviv, Tel Aviv, Israel, [3]Materno-Fetal and Obstetrics Research Unit, [4]Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [5]Centre Régional de Pharmacovigilance, Hospices Civils de Lyon, Lyon, France, [6]UKTIS, Regional Drug and Therapeutics Centre, Newcastle upon Tyne, United Kingdom, [7]Centro di Riferimento Regionale di Tossicologia Perinatale, Azienda Ospedaliero Universitaria Careggi, Florence, Italy, [8]Teratology Information Service, HUSLAB and Helsinki University Central Hospital, Helsinki, Finland, [9]Poison Control, Bergamo, Italy, [10]TIS Netherlands, Pharmacovigilance Centre Lareb, Den Bosch, [11]Unit of Pharmacotherapy & Pharmaceutical Care, Department of Pharmacy, University of Groningen, Groningen, The Netherlands, [12]The Motherisk Program, The Hospital for Sick Children, Toronto, ON, Canada, [13]Centre de Pharmacovigilance de Tours, CHRU, Tours, France, [14]Faculty of Medicine, Department of Pharmacology, Karadeniz Technical University, Trabzon, Turkey

Introduction: The Swiss Teratogen Information Service (STIS) is dedicated to providing evidence-based information to health care professionals about medications and other exposures during pregnancy. By collecting data on cases of exposure which are reported to our service, as well as the outcome of pregnancy or any effects on the child, we contribute to research in the field of teratology. By pooling and analysing data collected by Teratology Information Services in different countries, we organise studies addressing risks associated with medication poorly characterised regarding reproductive safety. In this study we present the results of the first prospective cohort study on pregnancy outcomes after maternal treatment with pregabalin.
Methods: This is a multicenter, observational prospective cohort study comparing pregnancy outcomes in women exposed to pregabalin with matched controls (exposed neither to any medications known to be teratogenic nor to any antiepileptic drugs). Data were systematically collected by Teratology Information Services between 2004 and 2013.
Results: We obtained data from 173 exposed pregnancies and 692 controls. After exclusion of chromosomal syndromes, major birth defects were reported more frequently in pregnancies exposed to pregabalin during 1st trimester of pregnancy than in the control group (6.6% versus 2.0%; odds ratio 3.5, 95% confidence interval 1.2-9.7, $p = 0.004$). Moreover, the rate of live births was lower in the pregabalin group (71.1% versus 85.4%, $p < 0.001$), primarily due to a higher rate of both elective (10.4% versus 4.8%, $p = 0.01$) and medically indicated (5.2% versus 1.7%, $p = 0.02$) pregnancy-terminations. The crude rate of spontaneous abortion (15.8% versus 8.7%, $p = 0.001$) was also higher in the pregabalin group.
Conclusions: This study raises a signal for a possible increase in the risk of major birth defects and spontaneous abortion after first trimester exposure to pregabalin. These results call for further confirmation through independent studies. By contacting STIS for advice concerning drug exposure during pregnancy, healthcare professionals in Switzerland can contribute significantly to knowledge in a field where maternal and fetal risks associated with many medications remain largely unknown.

P461 Coca-cola-induced effects on lithium and other psychopharmacological treatment

Etienne M. Grandjean[1], Jean-Michel Aubry[2]
[1]Internal Medicine and Clinical Pharmacology, Private Practice, [2]Service des Spécialités Psychiatriques - Unité des Troubles de l'Humeur, Hôpitaux Universitaires de Genève (HUG), Genève, Switzerland

Introduction: Unlike drug-drug interactions, food-drug interactions with lithium (Li) are rarely recognised and reported, although they may be highly relevant, resulting in increased Li elimination and therapy failure.
Case report: We report the case of a 59-year old male patient, known to have had bipolar disorder for 14 years. After his last stay in a psychiatric ward, he consulted one of us for a second advice regarding his treatment. During the 3 years before his last relapse, he had been treated with olanzapine and Li and had experienced weight gain of 14 kg and a mild diabetes. He was resentful about that and had stopped any treatment 5 months ago. 4 months later, he relapsed and suffered a hypomanic episode.
At our first visit, he had been released from the hospital with a treatment of olanzapine 15 mg and Li sulphate 24 mmol/day. He was concerned about a possible further weight gain. He also revealed that, during the last few years, he had been drinking at least 2 litres of coca-cola per day (192 g of caffeine and 210 g of carbohydrates [840 kcal] per day). He was a non-smoker, and did not regularly drink alcoholic beverages. The clinical examination was normal. Serum Li level was 0.37 mmol/L, with a dose of 12 mmol twice a day. The patient denied any lack of compliance. During the following days, he stopped consuming coca-cola, replacing it by 1 litre of syrup per day (110 g of carbohydrates). At 2 weeks, serum Li was 0.84 mmol/L with the same daily dose.
Discussion: Most interactions with Li result in a decreased renal clearance of Li and require a decrease in the daily dose, in order to prevent Li intoxication. Only mannitol, theophylline and caffeine are known to increase Li clearance. There are only few reports, however, to assess the clinical relevance of such interactions, especially with regard to nutritional habits. One case of heavy coca-cola zero drinking interfering with Li therapy has been published. The present case is a further example of such coca-cola/Li interaction.
Furthermore, the high caloric intake by carbohydrate-rich drinks may have played a role in the development of overweight and type 2 diabetes.
Conclusion: A high dietary intake of caffeine as coca-cola during Li therapy should be avoided, since it is likely to reduce Li efficacy, by increasing its clearance. Moreover, the high carbohydrate content of that beverage may play a role in the overweight associated with combined treatment with olanzapine and Li.

P462 Acute sirolimus overdose: a multicenter case series

Alessandro Ceschi[1,2], Elja Heistermann[3], Sonja Gros[4], Cornelia Reichert[1], Hugo Kupferschmidt[1], Stephan Krähenbühl[5], Anne Taegtmeyer[5]
[1]Swiss Toxicological Information Centre, Associated Institute of the University of Zurich, [2]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland, [3]Berlin Poison Information Centre, Berlin, [4]Mainz Poison Control Centre, Mainz, Germany, [5]Department of Clinical Pharmacology and Toxicology, University and University Hospital Basel, Basel, Switzerland

Background: There are few data relating to sirolimus overdose in the medical literature. Our objectives were to describe all cases of overdose with sirolimus reported to Swiss, German and Austrian Poisons Centres between 2002-2013.
Methods: An observational case-series analysis was performed to determine circumstances, magnitude, management and outcome of sirolimus overdose.
Results: Five cases of acute sirolimus overdose were reported - three in young children and two in adults. Four were accidental and one was with suicidal intent. Two patients developed symptoms probably related to sirolimus overdose: mild elevation of alkaline phosphatase, fever and gastroenteritis in a 2.5-year-old male who ingested 3 mg, and mild changes in total cholesterol in an 18-year-old female after ingestion of 103 mg. None of these events were life-threatening. Serial blood concentration measurements were performed

starting 24 h after ingestion of 103 mg in a single case, and these followed a similar pharmacokinetic time-course to measurements taken after dosing in the therapeutic range.
Conclusions: Acute sirolimus overdose occurred accidentally in the majority of cases. Even large overdoses appeared to be well-tolerated, however children might be at greater risk of developing complications. Further study of sirolimus overdose is needed.

P463 Generic medications in patients suffering from chronic musculoskeletal pain: representations, trust and prescription

Stephanie d'Incau[1], Valérie Piguet[2,3], Marie Besson[3], Jules Desmeules[3], Christine Cedraschi[2,4]
[1]Service de Médecine Interne et Générale, [2]Centre Multidisciplinaire de la Douleur, [3]Service de Pharmacologie et Toxicologie Cliniques, [4]Service de Médecine Interne et de Réhabilitation, Hôpitaux Universitaires de Genève (HUG), Genève, Switzerland

Introduction: Chronic pain patients are frequently confronted with the issue of the prescription and/or substitution of original formulations with generic medications. The review of the literature indicates that information regarding generic substitution is not univocal and room for the expression of contradictory opinions is ample. Along with an ever stronger advocacy for the use of generics, various sources of information report concerns regarding substitution.
Methods: Semi-structured interviews explored patients' representations regarding generics in patients suffering from chronic musculoskeletal pain. Patients' interviews were transcribed and submitted to content analysis.
Results: The representations of 25 included patients suggest that they might be confident in taking a generic medication: when a) he/she has an understanding of generics as resulting from a development process that has become part of the public domain; b) the generic medication is prescribed by the physician (supported by the pharmacist); c) each prescription is discussed, i.e., the patient is prescribed the generic version of a given medication and not a generic medication; and d) the prescription is individualized.
Information and trust are central considerations; the broad concept of “copy”, from an identical to a forged medication, was frequently mentioned to define generics. Using a copy might not be questioned when the medications are perceived as being identical and efficient; however, it might become a problem in cases in which the copy indicates that the patient thinks he/she is receiving a second-choice medication
Conclusion: The results of this study provide support for generic medication raising many concerns and much lesser perceived need. For patients, economic arguments per se are not sufficient to justify substitution. In this context, positive cues require further attention and negative cues need to be de-emphasized - in particular lower price as an indication of lower quality, and generic status as contradictory with advocating individualization of medication.

P464 Disseminated intestinal and gastric pneumatosis with portal vein gas in a patient treated with pazopanib for metastatic renal carcinoma

Jürgen Bohlender[1,2], Gael Rhyner-Agocs[1], Daniel Hayoz[1], Daniel Betticher[1]
[1]Clinique de Médecine, Hôpital Fribourgeois, Fribourg, [2]Department of Nephrology and Clinical Pharmacology, Inselspital, University of Bern, Bern, Switzerland

Introduction: Pazopanib is a new tyrosine kinase inhibitor used to treat metastatic renal cell carcinoma. It has numerous gastro-intestinal side-effects due to its broad interference with cellular growth signaling pathways. Intestinal pneumatosis is a rare complication of gas accumulating in the intestinal wall and associated with adverse outcome in the context of bowel ischemia or bacterial invasion. There are only a few published cases relating pneumatosis to tyrosine-kinase inhibitors and precise knowledge about this potentially fatal complication is lacking.
Case presentation: A 71 year-old male patient with metastatic renal carcinoma (tracheal/lung, liver, thyroid, vertebral, adrenal) diagnosed 9 years ago was admitted to our hospital after endotracheal stent replacement.

He had had unilateral nephrectomy and a therapy by bevacizumab and presented with renal insufficiency stage 2, substituted adrenal insufficiency and intermittent atrial fibrillation but no other relevant comorbidity. He had been treated by everolimus until 4 weeks before admission when pazopanib was started (800 mg/d) because of tumor progression. On admission, iv antibiotics were givien for suspicion of pulmonary infection. Serum transaminases, urea, bilirubin and coagulation tests were normal and serum CRP 60 mg/l, blood hemoglobin 99 g/l, leukocytes 7.3 G/l and thrombocytes 429 G/l. Blood pressure and heart rate were normal. Pazopanib was continued. He was afebrile on the 5th day when antibiotics were stopped. On the 8th day fever suddenly reoccurred and the patient complained of increasing abdominal pain. A CT scan showed disseminated intestinal and gastric pneumatosis, and the presence of gas in the portal, mesenteric and pericardial veins. There were signs of extended bowel and gastric ischemia without arterial or venous thrombotic occlusion. Serum lactate, CRP values and leukocyte count were significantly increased. The patient died of septic shock a few hours later.
Conclusion: Pazopanib may cause abnormal hemostasis and microangiopathy with hemorrhagic or ischemic organ complications. This may have precipitated gastro-intestinal ischemia, bacterial invasion and disseminated pneumatosis also in our patient. The rapidly fatal course of this rare complication warrants a high degree of clinical suspicion and surveillance in patients treated with this drug class including screening for and treatment of risk factors for bowel ischemia.

P464a Colistimethate sodium and colistin pharmacokinetics in ambulatory hemodialysis - a case report

Natascia Corti[1], S.W. Weiler[1], M.H. Hofer[2], T.H. Hess[2], S.W. Wehrli[2]
[1]Clinical Pharmacology and Toxicology, University Hospital Zürich, Zürich, [2]Department of Internal Medicine, Cantonal Hospital of Winterthur, Winterthur, Switzerland

Introduction: Colistin is a polymyxin antibiotic for the treatment of Gram-negative infections with concentration-dependent killing properties. A target plasma concentration > 2.5 mg/L has been suggested for most pathogens. 60%-80% of the prodrug colistimethate sodium (CMS) is excreted unchanged by the kidneys and the rest is hydrolyzed to its active form colistin. Dose reductions according to the degree of renal impairment are indicated. However, product information does not give dosing recommendations for intermittent hemodialysis (HD) and pharmacokinetic data of CMS and colistin in patients with severe renal impairment and HD with modern high flux filter are scarce.
Methods: Pharmacokinetics of Colistin and CMS were assessed in a 48 kg female patient with endstage renal disease. She was treated with Colistin® intravenously daily for chronic pulmonary infection with a multiresistant *Pseudomonas aeruginosa*.
1.5 million units (MioU) Colistin® were infused over 30 minutes after the end of each HD session and 1 MioU was administered on the day without HD. HD was performed as postdilution Online Hemodiafiltration with the polynephron highflux filter *Elisio 19H* with a surface of 1.9m2 for 4 hours. Peripheral blood samples were taken before and at the end of each Colistin® infusion with 3-4 samples taken additionally over the dosing interval to determine Cmin, Cmax, AUCt, clearance and elimination half life. HD clearance and fraction removed was additionally calculated. Plasma concentrations of CMS and free colistin were determined by liquid chromatography-mass spectrometry.
Results: Overall mean peak and trough concentrations of CMS were 20.4 mg/L and 3.1 mg/L, and of colistin 0.1mg/L and 2.2mg/L, respectively. Comparable colistin exposure was found during all three dosing intervals with steady plasma levels of 3.3-3.5 µg/mL of colistin on the non-HD day and 2.4-3.1 µg/mL on HD days. 71% - 75% of colistin was removed during a HD session. Colistin half life was 2.3 hours and mean HD clearance was 59 mL/min. Between HD sessions the plasma concentration time curve of CMS showed a rapid decline. Mean half life and clearance were 2 h and 20.2 mL/min for CMS, and 155 h and 1.5 mL/min for colistin, respectively.
Conclusion: Colistin is significantly removed by HD. Target colistin plasma concentrations of >2.5mg/ml were reached with a Colistin® dosing regimen of 1.5 MioU administered shortly after HD and 1 MioU administered on non-HD days.

P464b Autonomic, cardiovascular, and endocrine effects of LSD in healthy subjects

Matthias E. Liechti, Yasmin Schmid
Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Basel, Switzerland

Introduction: LSD is used recreationally worldwide and there is renewed interest in using LSD in clinical psychiatric research and practice. However, there is limited data on the somatic and endocrine effects of LSD in humans.
Method: LSD (200 µg) and placebo were administered to 16 healthy subjects (eight women, eight men) in a double-blind, randomized, placebo-controlled, cross-over study. Cardiostimulant effects (blood pressure and heart rate), autonomic effects (body temperature and pupillary function), endocrine effects, and adverse effects were repeatedly assessed.
Results: LSD induced positive mood, visual perceptual alterations, and audio-visual synesthesia lasting for 12h. LSD significantly increased blood pressure, heart rate, body temperature, and pupil size. LSD elevated the plasma concentrations of cortisol, prolactin, oxytocin, and epinephrine but not norepinephrine. LSD impaired psychomotor performance (balance) and produced adverse side effects (difficulty concentrating, headache, exhaustion, dizziness) up to 24 h, which completely subsided within 72 h. No severe acute adverse effects were observed.
Conclusion: The hallucinogen LSD produces significant sympathomimetic effects. The LSD-induced increase in cortisol and prolactin is consistent with LSD's serotonergic properties. The cardiostimulant properties of LSD need to be considered in patients with hypertension or heart disease.

P464c Vincristine-induced neuropathic pain in a CYP3A5 non-expresser with reduced CYP3A4 activity

Marija Bosilkovska, K. Ing Lorenzini, J. Desmeules, Y. Daali, M. Escher
Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland

Background: Vincristine is metabolised by CYP3A5 and CYP3A4 isoforms with CYP3A5 contributing to 75% of vincristine intrinsic clearance. Vincristine is a substrate of the P-glycoprotein (P-gp) transporter. An increase in vincristine neurotoxicity in CYP3A5 non-expressers has been observed. The severity of neuropathy was found to be inversely correlated to vincristine metabolite concentrations. However a clear correlation between genetic polymorphisms and vincristine toxicity has not been established.
Case presentation: We report the case of a 21-year old African male patient who received vincristine 2 mg on three occasions (on 14.10, 30.10 and 06.11.14) for the treatment of pre-B acute lymphoblastic leukemia. Six weeks after the last vincristine dose the patient complained of bilateral severe burning pain in the toes and allodynia, suggestive of neuropathic pain.
The patient was genotyped for CYP3A5 using a real-time PCR method as well as for ABCB1 (coding for P-gp) G2677T/A and C3435T SNPs. The results showed that the patient presented a CYP3A5*3/*3 polymorphism indicating that he did not express CYP3A5 enzyme. He was a homozygous 'wild type' carrier for ABCB1 SNPs.
Furthermore, CYP activity was evaluated using the Geneva phenotyping cocktail including midazolam as a probe for CYP3A4. The patient had a decreased CYP3A activity which could not be explained by the concomitant medication. Similarly he had no CYP3A inhibitor in his medication at the time he received vincristine.
Conclusion: The lack of CYP3A5 expression together with decreased CYP3A4 activity probably led to a decrease in vincristine clearance and to an increase in its plasma concentrations. It is a likely explanation for the occurrence of neurotoxicity in our patient despite the low doses of vincristine he received. In patients treated with vincristine, CYP phenotyping and genotyping could be crucial in preventing serious side effects.

P464d Innovative approach to blood sampling using dried blood spots. Application to pharmacokinetics and cytochrome P450 phenotyping

Marija Bosilkovska[1], J. Deglon[2], A. Thomas[2], C. Samer[1], J. Desmeules[1], Y. Daali[1]
[1]Geneva University Hospitals, Geneva, [2]University Center of Legal Medicine, Lausanne-Geneva, Switzerland

Background: Due to its numerous advantages such as low blood volume required, the simplicity of sampling from a small finger prick, the ease of storage, shipping and sample preparation, the use of dried blood spots (DBS) has gained in popularity in the last few years over conventional whole blood or plasma sampling for PK or drug monitoring. In order to overcome the impact that haematocrit has on the spreading of the applied drop of blood, precise knowledge of the collected volume is crucial for the determination of drug/metabolites concentrations.
Material and methods: Although the collection of an accurate capillary volume using a volumetric micropipette is simpler than venous blood collection, it still needs to be conducted by trained technicians using dedicated instruments. To simplify this process a new capillary blood collection device has been developed. The prototype integrates a patented microfluidic plate (WO/2013/144743) allowing for accurate volume control and a conventional filter paper card for blood storage.
The concentrations and pharmacokinetic profiles of a P-glycoprotein (P-gp) and six cytochrome P450 (CYP) probes and their metabolites obtained with the new sampling device have been compared with a conventional volumetric micropipetting method in a clinical trial including 30 volunteers who have received the Geneva cocktail for CYP and P-gp phenotyping. The cocktail was composed of: caffeine 50mg, bupropion 20 mg, flurbiprofen 10mg, omeprazole 10 mg, dextromethorphan 10mg, midazolam 1mg and fexofenadine 25mg as probes for CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A and P-gp respectively. The quantification was done using a previously validated LC/MS-MS method.
Results: Concentrations obtained with the new microfluidic sampling device showed excellent correlation with conventional micropipetting concentrations with slopes values close to 1 (0.91 - 1.03) and determination coefficients R^2>0.90 for all of the 13 analysed substances.
Sampling could be successfully performed by the volunteers themselves with almost no previous training.
Conclusion: DBS technique combined with an innovative sampling device and a sensitive analytical method can be used as a self-test for CYP and P-gp phenotyping
The use of this technique can be further enlarged to the quantification of other substances for PK studies and therapeutic drug monitoring.

P464e Metamizole-induced white blood cell disorders: a case-control study

Lea S. Blaser[1], Hala Hassna[1], Sarah Hofmann[1], Andreas Holbro[2], Manuel Haschke[1], Alexandra E. Rätz Bravo[1,3], Andreas Zeller[4], Stephan Krähenbühl[1], Anne Taegtmeyer[1]
[1]Division of Clinical Pharmacology and Toxicology, [2]Hematology and Blood Transfusion Center SRC, Head Stem Cell Lab, [3]Regional Pharmacovigilance Center, University Hospital Basel, [4]Centre for General Practice, University of Basel and Kantonal Hospital Baselland, Basel, Switzerland

Introduction: The aim of this study was to compare cases of metamizole-associated white blood cell disorders with a control group to identify probable risk factors for the development of such disorders and therefore to improve our knowledge about metamizole's risk-benefit profile.
Methods: A retrospective case-control study was performed. Cases of metamizole-associated white blood cell disorders managed at the University Hospital of Basel between 2005 and 2013 were characterized and compared to a control group consisting of patients from general practice settings who took metamizole for at least 28 days without complications.
Results: Fifty-seven cases of metamizole-induced white blood cell disorders were compared to a control group of 93 ambulatory patients from general practice settings. There were more women than men in both groups (63 and 70% respectively), indicating that female-sex is not a risk factor. The number of patients with a positive allergy history was higher in the case group ($p = 0.0174$) as was the number of patients with a preexisting hematological condition ($p = 0.0050$), in particular cytopenias ($n = 4$ among cases vs. 0 among

controls).
Conclusions: A positive allergy history and preexisting cytopenias are possible risk factors for metamizole-induced white blood cell disorders.

P464f Monitoring of azathioprine metabolite concentrations in autoimmune hepatitis

Ariane Züst[1], Alexander Jetter[2]
[1]Hospital Pharmacy, See-Spital Horgen, Horgen, [2]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zürich, Switzerland

Introduction: In the treatment of moderate to severe autoimmune hepatitis, the immunosuppressant azathioprine is added to corticosteroids to attain and to maintain remission. Azathioprine is a prodrug which is bioactivated to 6-thioguanine nucleotides (6-TGN) by a number of enzymatic steps, while competing steps lead to the potentially hepatotoxic, but therapeutically inactive methylmercaptopurine nucleotides (MMPN). Since these metabolic steps show large interindividual variabilities, partially caused by genetic variation in the activities of the enzymes involved, therapeutic monitoring of 6-TGN and MMPN in patients has been proposed, but there is continuing debate about its usefulness and therapeutic ranges.
Methods: In this retrospective cohort study, records of patients with autoimmune hepatitis who were treated at the University Hospital Zurich with azathioprine and in whom at least one quantification of 6-TGN and MMPN has been carried out between 2002 and 2013, were evaluated. The study was approved by the Ethics Committee of the Canton of Zurich. Only records of patients who had not refuses research access to their data were included. The main objectives were to find relationships between azathioprine doses, concentrations of 6-TGN and MMPN, and clinical outcome parameters. Remission status was assessed using clinical and laboratory information.
Results: Records of 19 female and 10 male patients with autoimmune hepatitis were included. The median age at diagnosis was 54 (range 17-77) years, the median dose of azathioprine was 2.03 (range 0.4-5.4) mg / kg bodyweight /day, and this dose had been maintained unchanged since a median of 8.75 (range 0-70) months. The median 6-TGN concentrations were 234.5 (range 50-896) pmol/8 x 10^8 red blood cells, median MMPN concentrations were 872.5 (range 100-13'664) pmol/8 x 10^8 red blood cells. Overall, there was no statistically significant correlation between azathioprine dose and 6-TGN concentrations, but a weak correlation between dose and MMPN concentrations was observed. For the entire group of patients, no relationship between 6-TGN concentrations and remission status was found, while in patients with liver cirrhosis, higher 6-TGN concentrations were associated with remission. No common therapeutic range for all patients with autoimmune hepatitis was substantiated.
Conclusion: This study underlines the complex association between azathioprine dose, metabolite blood concentrations and therapy response.

P464g Single-center, randomized, open-label, 3-way crossover study to characterize RAS-peptide-profiles after single and repeated oral administration of different RAS-inhibitors in healthy male subjects

Andrea Stoller[1], Marco Poglitsch[2], Massimiliano Donzelli[1], Stephan Krähenbühl[1], Manuel Haschke[1]
[1]Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Basel, Switzerland, [2]Attoquant Diagnostics GmbH, Vienna, Austria

Introduction: Angiotensin II (Ang1-8), the main effector of the renin-angiotensin-system (RAS) induces vasoconstriction, as well as sodium and water retention. Ang1-8 is degraded to smaller RAS peptides like Ang1-7 which mediates counter-regulatory effects. Cardiovascular drugs like renin- or ACE-inhibitors or angiotensin receptor blockers interfere at different levels of the RAS and are expected to cause characteristic alterations of RAS peptide concentrations. Drug specific alterations of RAS peptide profiles could be useful, e.g. to assess drug adherence or inter-individual differences in drug response. Therefore, the objective was to characterize RAS peptide profiles after treatment with three clinically used RAS inhibitors.

Methods: An open-label, single-center, randomized 3-way crossover study was conducted in 12 healthy normotensive male subjects. RAS peptide profiles were determined after single and repeated dose administration for 7 days of the renin-inhibitor aliskiren (150mg), the ACE-inhibitor enalapril (10mg) and the angiotensin receptor blocker losartan (50mg). Non-invasive blood pressure measurements and heart rate were recorded and concentrations of RAS peptides were determined using a liquid chromatography-tandem mass spectrometry method.
Results: Treatment with the three RAS inhibitors led to characteristic changes of the RAS peptide profiles already after the first dose and these characteristic profiles remained stable after one week of repeated dosing. Maximum effects were observed between 4 and 8 hours after drug administration, corresponding to the Cmax of the RAS inhibitors. While the renin inhibitor decreased all downstream RAS peptide concentrations, the ACE inhibitor caused a characteristic increase of upstream Ang1-10 and Ang1-7 levels and a decrease of Ang1-8 and Ang1-5 levels. Treatment with the angiotensin receptor blocker on the other hand increased both Ang1-10 and Ang1-8 levels, most likely due to enhanced renin-feedback.
Conclusion: Single and repeated dose treatment with the three different RAS inhibitors caused characteristic and stable changes of the RAS peptide profiles that reflected the different modes of action of the three different drug classes. RAS peptide profiles merit further evaluation as possible biomarkers e.g. to assess treatment adherence or to investigate differences in drug response in patients with arterial hypertension treated with such drugs.

P464h Evaluation of CYP450 and transporters expression and activity in HepaRG cell line in different conditions

Flavia Storelli, C. Bruggmann, F. Doffey-Lazeyras, C. Samer, J. Desmeules, Youssef Daali
Division of Clinical Pharmacology and Toxicology, University Hospitals of Geneva, Geneva, Switzerland

Introduction: HepaRG is a newly developed human hepatoma cell line which is able to differentiate to both hepatocyte-like and biliary-like cells after reaching confluence. When differentiated, HepaRG cells have shown good drug-metabolizing properties compared to primary human hepatocytes. Previous works have shown that confluent HepaRG cells start to differentiate when adding 2% DMSO in the culture medium. However, DMSO is well known to induce cell death.
Methods: In order to optimize CYP450 activity while decreasing cell apoptosis, we tested different culture conditions for differentiation by varying DMSO concentration from 0 to 2% and by adding growth factors EGF and HGF at concentrations of 10 ng/ml. CYP activity was assessed using a cocktail approach by LC-MS/MS. Expression of several CYP450, phase II enzymes UGT1A1 and UGT2B7 and various uptake and efflux transporters was assessed with Nanostring® technology. The culture media tested were all compared to differentiation medium MIL720 from Biopredic®.
Results: The higher DMSO concentration, the more differentiated cells were observed under microscopy. However, cell viability was significantly decreased when adding DMSO up to 2%. Considering CYP450 activity, DMSO increased significantly the activity of CYP3A4, 2B6 and 1A2. The addition of growth factors EGF and HGF was found to have a negative impact on cell differentiation and thus CYP activity, but significantly improved cell viability. There was a good correlation between CYP activity and CYP expression ($P < 0.05$) except for CYP1A2. In all conditions tested, CYP 2D6 showed a weak activity and expression levels were undetectable. UGT1A1 and UGT2B7 transcripts were found at appreciable levels and were influenced by DMSO concentration. Considering hepatic transporters, the same profile regarding influence of DMSO was observed. Efflux transporters MRP2, MRP3 and MDR1 (P-gp) levels were high, whereas BSEP, BCRP and MRP1 levels were low. Considering hepatic uptake transporters, OCT1 was largely expressed. OATP1B1, 2B1, OCT3, OAT2 expression was found in acceptable levels. On the contrary, NTCP and OATP1B3 transcripts were undetectable. Differentiation medium containing 1.5% showed similar viability compared to MIL720 from Biopredic used as reference, with slightly lower CYP450 activities. This medium was thus chosen for further metabolism experiments on the HepaRG cell line.

P464i In-vitro evaluation of DDI with cobicistat and ritonavir using HepaRG cell line

Flavia Storelli, C. Bruggmann, F. Doffey-Lazeyras, C. Samer, J. Desmeules, Youssef Daali
Division of Clinical Pharmacology and Toxicology, University Hospitals of Geneva, Geneva, Switzerland

Introduction: Cobicistat (Tybost®) is a new pharmacoenhancer which has recently been approved by the EMEA as a boosting agent for the HIV protease inhibitors atazanavir and darunavir. As opposed to ritonavir, a protease inhibitor used as a boosting agent in HIV treatment combinations, cobicistat does not show any antiviral activity. Also, previous inhibition studies on human hepatic microsomal fractions showed a more specific inhibition of CYP3A4 of cobicistat versus ritonavir and a lack of induction potential on CYP3A4.
Methods: The aim of this work was to investigate CYP450 inhibition/induction potential of major CYPs by cobicistat and ritonavir in HepaRG. On this purpose, low density-seeded confluent HepaRG cells were differentiated in a culture medium containing 1.5% DSMO and plated in 24-well plates. At day 12 after plating, cobicistat or ritonavir both at various concentrations ranging from 0 to 50 microM were incubated with a probe cocktail composed of midazolam 5 microM (CYP3A4), S-mephenytoin 50 microM (CYP2C19), bupropion 50 microM (CYP2B6) and flurbiprofen 10 microM (CYP2C9). Metabolite production after 3 hours of incubation at 37°C was quantified by LC-MS/MS and IC50 were calculated by linear regression. For induction assay, cobicistat or rifampicin for positive control at various concentrations ranging from 0 to 50 microM were incubated with HepaRG cells for 72 hours in a medium composed of 0.5% DMSO and deprived of FBS. DMSO concentration was decreased from 1.5 to 0.5 % 24 hours before addition of the inducers. CYP3A4 activity was assessed by incubation of midazolam 5 microM for 3 hours at 37°C and quantification of metabolite production by LC-MS/MS.
Results: Cobicistat and ritonavir showed similar inhibition of CYP 3A4 with IC50 of 0.107 microM and 0.105 microM respectively. IC50 values of CYP 2B6, 1A2, 2C19 and 2C9 were lower for cobicistat than for ritonavir, thus suggesting that cobicistat may be a more potent inhibitor of these CYP450 than ritonavir. Considering CYP3A4 induction, cobicistat did not seem to induce CYP 3A4. Rifampicin, which was used as a positive control, showed induction of CYP 3A4 up to 2.5 fold.
Conclusion: This work has showed the suitability of the HepaRG cell line to study inhibition drug interactions *in vitro*. Induction assays however have still to be optimized to reach greater levels of induction.

P464j New Year's resolutions and new lifestyle drugs: consider interactions

Hendrike Dahmke[1], Hugo Kupferschmidt[2], Gerd A. Kullak-Ublick[1], Stefan Weiler[1]
[1]Department of Clinical Pharmacology and Toxicology, Regional Pharmacovigilance Centre Zurich, University Hospital Zurich and University Zurich, [2]Associated Institute of the University of Zurich, Tox Info Suisse, Zurich, Switzerland

Introduction: Nalmefene (Selincro®) is a selective opioid receptor antagonist, which was licensed in April 2014 in Switzerland for the reduction of alcohol consumption in adults at a high drinking risk level. Due to its pharmacodynamics mechanism concomitant use of nalmefene and opioids should be avoided and nalmefene is contraindicated in opioid dependence or abuse.
Methods: Four cases of nalmefene combined with opiods were reported to the regional pharmacovigilance centre of Zurich accumulating in a temporal correlation around New Year. A systematic search for reported adverse drug reactions of nalmefene was conducted in the WHO global database VigiLyze™ until 2015-03-01. Individual case safety reports from 200 individuals were analysed.
Results: In three patients on methadone and in one patient on oxycodone the use of nalmefene led to withdrawal symptoms including agitation, emesis, myoclonus, tremor, nausea. Symptoms occurred shortly after the first intake of nalmefene. Overall in the WHO database of adverse drug reactions 200 reports on nalmefene were identified wordwide. The majority of patients was aged between 45 and 64 years (105, 53%), 135 patients (68%) were male. In 21 cases nalmefen and an opioid were administered concomitantly (13 with methadone, 1 with morphine, 1 with fentanyl, 2 with buprenorphine, 2 with codeine and 2 with oxycodone). Only three patients, who had any of these combinations were female (14%), the median age was 44 years (min 28, max 66). In 15 cases the terms “opiate withdrawal symptoms”, “withdrawal syndrome” or “drug withdrawal syndrome” were coded.
Conclusions: The coadministration of nalmefene and opioids should be avoided as withdrawal symptoms

may occur by competitive binding at the opioid receptor. Patients should be asked about opiate consumption before starting nalmefene due to co-occurrence of substance use disorders and alcohol dependence. Adverse drug reactions concerning new drugs licensed in the last 5 years should be reported to the regional pharmacovigilance centres.

Gastgesellschaft: Poster SGKPT

Société conviée: Session de poster SSPTC

P465 Electronic vigilance reporting portal

Thomas Schwartz, Martina Schäublin, Christoph Küng
Swissmedic, Bern, Switzerland

The spontaneous reporting of suspected adverse drug reactions (ADR) remains the most important tool for identifying new medicinal product risks that come to light after market launch and learning more about risks that are already known. Information technology has made an important contribution to the establishment and rapid development of these reporting systems in recent years.
However, a spontaneous reporting system can only provide a successful risk defence tool if physicians, pharmacists and other Health Care Professionals (HCP) play an active role in it, since new findings on the safety of medicines are derived primarily from a detailed analysis of carefully documented individual cases. Since October 2014, Swissmedic´s Electronic Vigilance System ElViS has been available for directly reporting suspected ADR on the internet. HCP who have hitherto been using reporting forms to notify the Regional Pharmacovigilance Centers of suspected cases can now do so online. Moreover, pharmaceutical companies with no direct gateway connection to the Swissmedic database (usually small and medium-sized companies), can also submit their reports electronically to Swissmedic. No special software is required, and only a few minutes are required to complete the one-time self-registration process for HCP. ElViS can also be used to submit case-related documents, such as laboratory reports or hospital discharge reports. Attachments can be in any file format. Once their report has been successfully sent, users can save the report and acknowledgement of receipt (in E2B format or as pdf) on their computer´s hard drive for their own records. Data protection and security satisfy the most stringent requirements. ElViS is available to HCP in four languages.
In the first three months since ElViS was launched, around 70 HCP and almost 40 companies have registered. Approximately 100 suspected ADR have been reported.
This is a very encouraging result and proves that the new user-friendly way of reporting ADR is making a further contribution to improving drug safety. The people responsible for ElViS hope that it will intensify communication, improve reporting among HCP and enhance the quality of reports (completeness and plausibility).

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