31e Internistendagen

ABSTRACTBOEK

(Abstracts submitted to the Annual Meeting of The Netherlands Association of Internal Medicine, 24-26 April 2019, Maastricht, The Netherlands)

24-26 April 2019
MECC • Maastricht
Voorbereidingscommissie
Dr. P.M. Stassen, voorzitter
Dr. M.P. Bauer
M.A.C. van Haaren, JNIV
Dr. C.P.C. de Jager
Dr. R.J.W. van Kampen
Dr. ir. J. Lagro
Prof. dr. S. Middeldorp
Dr. C. van Noord
M.E.M. Rentinck
Dr. A. Rutgers
Dr. J.C. Verhave
Drs. B.X. Oude Elberink, NIV Bureau – directeur
T.C.B.M. van Waterschoot, NIV Bureau

Organiserende vereniging
Nederlandse Internisten Vereniging (Medicinae Internae B.V.)
Postbus 20066
3502 LB Utrecht
Tel: 030-282 32 29

Congressecretariaat
Congress Company Academy
Postbus 2428
5202 CK ’s-Hertogenbosch
Tel. 073-700 35 00
E-mail: info@congresscompany.com

Uitgever
MacChain
Postbus 330
1960 AH Heemskerk
Tel. 06-25056091
E-mail: info@macchain.nl
I Oral Presentations

- **O1.01** An important novel physiological observation: the PaO2/FiO2 ratio, a widely used index to assess lung injury, is influenced by the set FiO2
- **O1.02** Warming up to a cold Christmas: a couple with seasonal polycythemia disorder
- **O1.03** Age-related difference in healthcare use and costs of patients with chronic kidney disease and matched controls: analysis of Dutch healthcare claims data
- **O1.04** MGUS with significant impact
- **O1.05** Epileptic insults with behavioral changes and a normal EEG
- **O1.06** The erythrocyte sedimentation rate as a clue for hyperviscosity syndrome
- **O1.07** The patient’s perspective on improving the quality of acute medical care: determining Patient Reported Outcomes
- **O2.01** Rare adverse event: gastro-intestinal bleeding caused by deposition of sevelamer crystals
- **O2.02** Abscopal effect of nivolumab in Hodgkin Lymphoma
- **O2.03** Body Weight Course in the DiaBetes and LIfestyle Cohort Twente (DIALECT-1) - a 20-year observational study
- **O2.04** Scombroid poisoning in a general hospital restaurant
- **O2.05** Hospitalisation of adult influenza patients costs the Dutch healthcare system annually 28 million euros
- **O2.06** Prediction of 30-day mortality in older medical emergency department patients
- **O2.07** An unusual case of panhypopituitarism
- **O3.01** Upper leg amputation as treatment for pulmonary oedema in a patient with autonomic dysreflexia
- **O3.02** A rare cause of hemorrhagic diathesis
- **O3.03** A Pot Luck Dinner
- **O3.04** Psychosis due to polycythemia vera
- **O3.05** Recurrent abdominal catastrophe, hypertension and renal failure apparent following resection of a pituitary adenoma
- **O3.06** Severe systemic disease explained by the versatile role of interleukin-6, so time to switch it off
- **O3.07** Palmar fasciitis and polyarthritis syndrome: a rare paraneoplastic syndrome in patients with prostate carcinoma
- **O4.01** Incidence of cardiotoxicity over time in patients with HER2-positive metastatic breast cancer on long term treatment with trastuzumab and the potential risk factors
- **O4.02** The association between the APOP screener and relevant clinical outcomes at different timepoints in older patients acutely hospitalized for internal medicine
- **O4.03** Toxic Thyroid Nodules treated with Radiofrequency Ablation
04.04 Implementation of a preoperative multidisciplinary team approach to improve outcome in frail elderly colorectal cancer patients

04.05 Family gift

04.06 Urea as second-line treatment for hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion: a case series involving 13 in-hospital patients

04.07 A Complementary Complication

05.01 Physical activity after eating: sometimes a shocking combination!

05.02 Pitfalls of molecular diagnostic testing for Coxiella burnetii DNA on throat swabs

05.03 High epidemic burden of RSV disease coinciding with genetic alterations causing amino acid substitutions in the RSV G-protein during the 2016/2017 season in the Netherlands

05.04 Modified Ultrasound-guided Ethanol Ablation for Symptomatic Thyroid cysts

05.05 Hypokalemia and peripheral edema in a patient with metastatic prostate cancer

05.06 Alkaptonuria diagnosed in three siblings: Case report

05.07 The haarlem study: a cohort of 100 male amateur athletes using anabolic androgenic steroids. Study design and baseline characteristics

II Acute Medicine

P001 Factors affecting emergency department length of stay for internal medicine patients

P002 Roles and responsibilities of internists and Emergency Physicians at Dutch Emergency Departments: an explorative study

P003 A case of severe hypophosphatemia due to hyperventilation

P004 Polycythemia caused by chronic carbon monoxide poisoning due to shisha (water pipe) use

P005 Bicytopenia and myelopathy caused by dietary copper deficiency

P006 Funduscopie: yes or no? Hypertensive crisis and retinopathy in the emergency care setting; a retrospective cohort study

P007 Evaluation of blood culture epidemiology and efficiency in a large European teaching hospital

P008 Severe hemolytic anemia due to transient acquired G6PD deficiency after ingestion of sodium chlorite

P009 Synthetic cathinones among novel psychoactive substances: two patients with psychosis after chloromethcathinone use

P010 Fatal error or game fix? Cognitive overload and learning potential of the serious game DiagnostiGo

P011 Toxin-induced haemolysis secondary to Clostridium Perfringens

P012 Health related Quality of Life in sepsis survivors

P013 Severe sepsis or heroin intoxication? The use of heroine metabolites in clinical practice; a case report

III Diabetes Mellitus

P014 Early worsening of diabetic retinopathy in a pregnant patient: an eye-opener

P015 Environmental co-exposure to cadmium and lead and the association with diabetic kidney disease; another reason to avoid smoking and alcohol intake in patients with T2DM?
IV Endocrinology
- Po16 Learning Curve of Ultrasound-guided Radiofrequency Ablation for Symptomatic, Benign, Non-Toxic Thyroid Nodules
- Po17 Warning: Energy overload! Locate the source and reduce power
- Po18 Ultrasound-guided Core Needle Biopsy for Thyroid Nodules Improves Diagnostic Yield
- Po19 Nausea due to hypercalcemia?
- Po20 Intracerebral haemorrhage as presenting symptom of Conn’s syndrome
- Po21 Granulomatous mastitis; inflammation with a pituitary origin?
- Po22 Treatment of Severe Hypotonic Hyponatremia: Efficacy and Safety of 100 or 250 ml NaCl 3.6%
- Po23 An extreme case of polyuria
- Po24 Re-evaluation of Plummer’s High Dose Iodine Therapy as Last Resort Treatment for Graves Hyperthyroidism

V Gastro-Enterology
- Po25 Endoscopic evaluation in patients with newly diagnosed iron deficiency anemia
- Po26 Treatment of Severe Protein Malnutrition after Bariatric Surgery
- Po27 Severe complication of thiopurine treatment in a young woman with Crohn’s disease
- Po28 Supportive treatment of life-threatening upper gastro-intestinal bleeding in a Jehovah’s Witness with acute liver failure

VI General Internal
- Po29 A calcifying diagnosis
- Po30 Unexpected cause of abdominal pain in pregnancy
- Po31 General practitioner use of internal medicine e-consultations
- Po32 Increased erythrocyte sedimentation rate ‘e causa ignota’ for years; an unexpected twist to the story
- Po33 Dysphagia with a rare cause
- Po34 Markedly elevated vitamin B12; true or false?
- Po35 Co-trimoxazole induced hyperkalemia and potassium monitoring in hospitalized patients
- Po36 Validity and Diagnostic Overlap of Functional Somatic Syndrome Diagnoses
- Po37 A Dens Fracture Case Solved
- Po38 The use of human neutrophil elastase to differentiate cocaine-induced midline destructive lesions from granulomatosis with polyangiitis
- Po39 Drug-induced liver injury (DILI) associated with whey protein: ‘shake it off!’
- Po40 A red and swollen face after raising the arms
- Po41 An uncommon cause of pleuritic chest pain
- Po42 Neutropenia due to colchicine
- Po43 Trial by Ordeal
VII Geriatric Medicine

- P044 Reduced grip strength and gait speed in elderly are related to adverse outcomes

VIII Haematology

- P045 Efficacy and safety of octreotide as treatment for severe gastrointestinal bleeding in hereditary hemorrhagic telangiectasia patients: results of a prospective phase II clinical trial
- P046 Extensive bleeding after bone marrow biopsy: temporary acquired von Willebrand syndrome
- P047 Pancytopenia, panhypopituitarism and hypoxemia caused by intravascular large B-cell lymphoma
- P048 Nature x Nurture = Ageing2
- P049 The Great Imposter
- P050 Posterior reversible encephalopathy syndrome
- P051 (No) needle in a haystack?
- P052 Is first-line R-CHOP always a good idea? A >10-year population-based cohort identify ‘real-world’ diffuse large B-cell lymphoma patient subgroups in need of new upfront therapies

IX Immunology/Allergology

- P053 Eosinophilia in a patient with MPO-ANCA vasculitis: not always an obvious diagnosis
- P054 An aggressive unknown side effect of PCSK9 inhibition?
- P055 Man in the Bubble – No Access to Vitamin C
- P056 Persistent parvovirus B19 viremia associated chronic fatigue syndrome
- P057 Be aware of nitrofurantoin hypersensitivity reactions

X Infectious Diseases

- P058 In chronic Q fever patients MMP1 single nucleotide polymorphism (SNP) rs17125062 is inversely associated with complications and P2RX7 SNP rs3751143 is associated with therapy failure
- P059 Outpatient Parenteral Antimicrobial Therapy (OPAT): clinical experience from a secondary referral teaching-hospital
- P061 External validation and update of prognostic models to predict poor outcomes in hospitalized adults with RSV: a retrospective Dutch cohort study
- P062 An unfortunate rain barrel
- P063 Determining the causative agent and optimal duration of antibiotic therapy in patients with diabetes and foot osteomyelitis: BonE BiOPsy (BeBoP)-trial
- P064 Two diagnoses?
- P065 More than five years after the Dutch Q fever outbreak: Chronic Q fever has not disappeared
- P066 Complicated soft tissue infection after laser prostatectomy
- P067 Guinea pig: friend or foe?
- P068 A pain in the neck: searching in vein?
P069 Intentional overdose of dolutegravir/abacavir/lamivudine (Triumeq) in a 26-year-old man

P070 A special birthday present from your girlfriend

P072 A woman with Parrots Disease

P073 Acute cholecystitis went viral

P074 Cat Scratch Disease causing Cerebral Venous Sinus Thrombosis?

P075 A patient with AIDS and ...

P076 Successful treatment of chronic hepatitis E infection with pegylated-interferon-alpha in a immunodeficient patient with ribavirin treatment failure

P077 A patient with fever and skin lesions after vacation in South Africa

P078 Tetanus after inadequate post-exposition prophylaxis in an unvaccinated patient

P079 Two cases of HHV-6 encephalitis after stem cell transplantation

P080 Itch from Down Under

P081 More targeted use of oseltamivir and in-hospital isolation facilities after the implementation of a rapid molecular diagnostic panel for respiratory viruses in immunocompromised adult patients

XI Intensive Care

P082 Acute monocytic myeloid leukemia complicated by tumor lysis, renal failure and respiratory distress: thoughts on CVVH

P083 The triad of diabetic ketoacidosis, severe hypertriglyceridemia and pancreatitis in de novo diabetes

P084 Acute-on-chronic lithium intoxication

XII Nephrology

P085 Concomitant periarteritis nodosa and complement factor H deficiency in a patient with acute renal failure and adenocarcinoma of the lung

P086 Staphylococcus-associated glomerulonephritis: a clinical diagnosis

P087 Bisphosphonate nephropathy: a case series

P088 A Cold Case: Monoclonal Gammopathy of Cutaneous Significance

P089 Secondary hyperoxaluria due to pancreatic insufficiency

P090 An Unusual Cause and Presentation of Nephrotic Syndrome

P091 From obese to rare: A case of fibrillary glomerulonephritis

P092 Diuretic induced hypophosphatemia

P093 Performance and pitfalls of the fresenius® body composition monitor for water balance management in patients on hemodialysis

P094 Delayed onset of severe hypercalcemia in a patient with rhabdomyolysis-induced acute kidney injury

P095 Treatment of tubulointerstitial nephritis in Sjögren’s syndrome with cyclophosphamide: a case-report

P096 Linking weight loss and hypoalbuminemia in a patient with malignant pleural mesothelioma

P097 Hypercalcemia as presenting symptom of IgG4 related disease
XIII Oncology
- P098 A seizure treated with antibiotics
- P099 Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer; the COLOPEC randomized trial
- P100 Dizziness as a first manifestation of ovarian cancer
- P101 The relevance of geriatric assessment for elderly patients receiving palliative chemotherapy
- P102 Cyclophosphamide-induced severe symptomatic hyponatremia: a case report
- P103 Hypercalcemia in endometrial cancer: a bad omen
- P104 A rare presentation of metastatic breast cancer
- P105 Mornings are the worst: adverse event of pembrolizumab

XIV Other
- P106 Topiramate intoxications – Literature review and the first case report of a massive suicidal intoxication with toxicokinetic data following hemodialysis
- P107 Physician Suicide: A Scoping Review
- P108 An uncommon case of hematotherax

XV Reumatology
- P109 Prediction of organ involvement and survival in systemic sclerosis patients in the first 5 years from diagnosis
- P110 Prevalence and management of cardiovascular risk factors in ANCA-associated vasculitis: a cross-sectional study in the Netherlands and Canada
- P111 Hypertensive emergency as a manifestation of systemic sclerosis
- P112 It's never PAN... or is it?

XVI Vascular Medicine
- P113 Do we reach LDL-c treatment targets in patients with heterozygous Familial Hypercholesterolemia in the Netherlands?
- P114 Dalteparin and anti-Xa: a complex interplay of therapeutic drug monitoring
- P115 Extended anticoagulation for unprovoked venous thromboembolism: a survey on physicians' considerations and guideline adherence
- P116 Determination of the value of color Doppler ultrasound in patients with a clinical suspicion of giant cell arteritis
- P117 Thrombin generation is associated with bleeding risk in patients on dual antiplatelet therapy
- P118 The inflammatory and atherosclerotic profile of patients with primary hyperaldosteronism
An important novel physiological observation: the PaO₂/FiO₂ ratio, a widely used index to assess lung injury, is influenced by the set FiO₂

Amsterdam University Medical Centers, location VU Medical Center, Department of Intensive Care, Amsterdam

Background: The PaO₂/FiO₂ (P/F) ratio is the index of the arterial partial pressure of oxygen (PaO₂) and the fraction of inspired oxygen (FiO₂). The P/F ratio is widely used to assess the severity of lung injury. Conceptually, the P/F ratio should be independent of the FiO₂ and solely depend on the pulmonary condition. The variability in P/F ratio with modulation of FiO₂ is already predicted in mathematical models. However, it is not studied in patients yet. The purpose of the present study was to investigate the relationship between FiO₂ and the P/F ratio in mechanically ventilated patients.

Methods: In an interventional study 10 post-cardiac surgery patients were included. The P/F ratio was determined at FiO₂ levels ranging from 0.21 to 1.0 with 10 minute intervals. To understand the physiological effects of FiO₂ modulation on gas exchange and hemodynamics, mixed venous oxygen saturation, cardiac output and shunt fraction were assessed.

Results: Modulation of FiO₂ had a significant effect on the P/F ratio and on shunt fraction, both exhibiting a U-shaped pattern (P < 0.05). The median difference in P/F ratio between lowest and highest FiO₂ was 61mmHg (SD 77.95, 95% CI: 5.2–116.7, P = 0.035). Cardiac output was not significantly affected by FiO₂.

Conclusion: In contrast to current thinking, the FiO₂ has a significant and clinically relevant effect on the P/F ratio. The influence of FiO₂ on the P/F ratio is an important and novel physiological observation. It can lead to over- and underestimation of lung injury severity.
Warming up to a cold Christmas: a couple with seasonal polycythemia disorder

T.C. Arkesteijn¹, K.W. ter Horst¹, M.G.M. Buck², M.E.M. Rentinck³
¹Tergooi ziekenhuis, Afdeling Interne geneeskunde, Hilversum, ²Maatschap Huisartsen Frederik van Eeden, Huisartsgeneeskunde, Hilversum

Cases: In December 2018, just before Christmas, a 68-year-old man visited his general practitioner with headaches. Blood tests showed polycythemia (hemoglobin level 11.3 mmol/L). In the previous year at the end of the winter, he presented with headaches, dizziness, visual impairment, and syncope. Neurological and cardiac evaluation, including brain MRI and EKG, did not identify a cause. His symptoms subsided over the following months. Laboratory analysis in the previous year showed hemoglobin levels of 11.5 mmol/L in April and 9.8 mmol/L in August. During the same December month, his 71-year-old wife presented with malaise and myalgia. Her blood showed a similar pattern of elevated (10.7 mmol/L), normalized (8.8 mmol/L), and elevated (10.8 mmol/L) hemoglobin levels in April, August, and December, respectively.

Upon hearing of these cases, we suspected carbon monoxide poisoning. Laboratory analyses showed carboxyhemoglobin percentages of 26.9% (man) and 28.8% (woman). Inspection of their home by the fire department revealed elevated carbon monoxide levels, and the couple was forced to evacuate their home on Christmas Eve.

Discussion: Carbon monoxide intoxication is characterized by hypoxemia and tissue hypoxia due to the formation of carboxyhemoglobin. Symptoms are usually nonspecific and often misdiagnosed. Hypoxemia in the context of chronic exposure stimulates erythropoiesis, which may cause secondary polycythemia. Exposure is more common in winter due to increased use of fuel-burning appliances and poor ventilation. Clinicians should suspect chronic or subacute carbon monoxide poisoning in patients with unexplained polycythemia, especially when it is cold outside.
Age-related difference in healthcare use and costs of patients with chronic kidney disease and matched controls: analysis of Dutch healthcare claims data

M.J.M. van Oosten
Amsterdam UMC - locatie AMC, Afdeling Nefrologie - Medische Informatiekunde, Amsterdam

Background: The financial burden of chronic kidney disease (CKD) is rising due to the ageing population and increased prevalence of comorbid diseases. Our aim was to evaluate age-related differences in healthcare use and costs in stage G4/G5 CKD without renal replacement therapy (RRT), dialysis and kidney transplant patients and compare them to the general population.

Methods: Using Dutch healthcare claims we identified renal patients and divided them in 3 groups, i.e. CKD stage G4/G5 without RRT, dialysis and kidney transplantation. We matched them with two controls per patient. Total healthcare costs and hospital costs related and unrelated to CKD treatment are presented in three age categories (19-44, 45-64 and ≥ 65 years).

Results: Healthcare costs of patients did not differ as much between age categories as in controls. The majority (> 70%) of CKD stage G4/G5, transplant and dialysis patients used hospital care additional to CKD treatment compared to 30% of controls. Hospital costs unrelated to CKD treatment were highest in dialysis patients compared to CKD stage G4/G5 and transplant patients. For both total costs and costs unrelated to CKD treatment the ratio between patients and controls was highest in young patients.

Conclusion: Healthcare costs were higher in renal patients than in controls and cost ratios were highest at a young age. Additional costs were substantial even for patients with CKD stage G4/G5, as so for patients at a younger age, which may reflect that the burden of comorbidities is already present in advanced CKD patients and at a young age.
MGUS with significant impact

B.A. Snijer, H.J. Jansen, M. van Apeldoorn
Jeroen Bosch Ziekenhuis, Afdeling Interne geneeskunde, 's-Hertogenbosch

Case: A 77-year old Caucasian female with no relevant medical history and no relevant family history was referred to the Emergency Department on suspicion of angioedema without a provoking factor. She had swelling of the face, lips, oropharynx and larynx and was unable to swallow saliva. There was no swelling of the tongue, rash, hives or pruritus. Patient was admitted to the ICU for observation and treated with 1000 units of complement C1-esterase inhibitor (Cinryze®), which effectively reversed the angioedema. Blood results showed a normal complete blood count, monoclonal free light chains type lambda and decreased C3, C4 and C1-inhibitor function. Bone marrow biopsy revealed 9% monoclonal plasma cells, which confirmed the diagnosis light-chain monoclonal gammopathy of undetermined significance (MGUS). After the first episode there were multiple relapses of angioedema involving the face and the limbs, effectively treated with Cinryze®. Since the start of prophylaxis to prevent angioedema episodes with danazol there were no relapses any more.

Discussion: Acquired angioedema due to deficiency of C1-esterase inhibitor is a rare syndrome of recurrent episodes of angioedema, without urticaria or pruritus. It is typically occurring in older patients and is frequently associated with underlying disease, including MGUS. Treatment of acute attacks with complement C1-esterase inhibitor (Cinryze) is effective in the majority of patients. Long-term prophylaxis to prevent angioedema episodes include attenuated androgens, such as danazol, controlling symptoms in approximately one-half of patients.

Conclusion: Acquired angioedema caused by C1-inhibitor deficiency due to a light-chain monoclonal gammopathy of undetermined significance.
Epileptic insults with behavioral changes and a normal EEG

D. Kremer¹, F.W. Visser²
¹Ziekenhuisgroep Twente, Afdeling Interne Geneeskunde, Almelo, ²Ziekenhuisgroep Twente, Almelo

Case: A 69-year old Caucasian female with no relevant medical history, experienced personality changes and episodes of abnormal behavior, including frequent groaning, rapid tonic-clonic movements, urine incontinence and postictal amnesia since 5 months. These nightly attacks resolved spontaneously after 5-15 minutes. Afterwards, the patient ate something to feel better. She was diagnosed with epilepsy by a neurologist, despite the lack of abnormal findings on MRI-brain and EEG. Anti-epileptic drugs were started, but had no effect on the frequency of attacks.

After a new episode, the patient’s diabetic husband home-measured the patient’s serum glucose, which was 2.1 mmol/l (reference: 4.0 to 6.1 mmol/L). At admission low serum glucose levels were confirmed, and in a clinical fasting-test glucose levels dropped from 5.2 mmol/L to 1.9 mmol/L in less than 3 hours. Plasma levels of C-peptide and insulin were 540 pmol/L and 72.2 pmol/L respectively, resulting in an insulin/C-peptide ratio of 0.133. Our suspicion of insulinoma was confirmed by CT which showed an 11.1 mm diameter hypervascular mass in the pancreas.

This benign insulinoma was surgically removed with a partial pancreatectomy. The patient recovered fully with stable glucose levels, disappearance of her abnormal behavior and no ‘epileptic attacks’. Anti-epileptic drugs could be stopped.

Discussion: This case shows that a diagnosis of epilepsy can be wrongly made, especially when additional testing does not confirm the diagnosis. When accompanied with neuropsychiatric symptoms an insulinoma should be considered.
The erythrocyte sedimentation rate as a clue for hyperviscosity syndrome

Tergooi Ziekenhuis, Afdeling Interne Geneeskunde, Hilversum

Case: A 48-years old female with a history of hypertension was separately referred to the departments of internal medicine, gynaecology and ophthalmology because of various symptoms. She had complaints of painless bilateral blurred vision, headaches and spontaneous vaginal blood loss. Fundoscopy showed large retinal bleeding and tortuous vessels. Because of her history, an initial diagnosis of essential hypertension with secondary retinopathy was made. A standard blood analysis showed no anomalies, but her erythrocyte sedimentation rate (ESR) could not be determined by the Alifax analyzer. Crossmatching in the gynaecological work-up also revealed irregular antibodies.

The patient was treated by the internal medicine doctor with amlodipine/valsartan and the blood pressure effectively decreased. However, fundoscopy six weeks later showed no improvement. This observation initiated further analysis, revealing increased protein levels (129 gram/L) with IgM levels of 98 gram/L, supporting a diagnoses of hyperviscosity syndrome due to Waldenström macroglobulinemia. She was treated with high dose dexamethasone and plasmapheresis, which immediately improved her vision. After two sessions of plasmapheresis, the IgM had been lowered sufficiently. Waldenström macroglobulinemia was later confirmed by bone marrow biopsy.

Discussion: This case is of interest, as the combination of observations and investigations by different specialisms led to the diagnosis. The error in the ESR analyzer was due to ‘no flow’, which was in retrospect the result of the high blood viscosity. The ESR was repeated using the old Westergren method, showing a high ESR as well as aggregation of erythrocytes, making the disease visible to the naked eye.
The patient’s perspective on improving the quality of acute medical care: determining Patient Reported Outcomes

M.N.T. Kremers¹, T. Zaalberg², E.S. van den Ende², M.L.H. van Beneden², F. Holleman¹, P.W.B. Nanayakkara², H.R. Haak²

¹Maastricht University, Department of Health Services Research, and CAPHRI School for Public Health, Maastricht, ²Máxima Medisch Centrum, Afdeling Interne Geneeskunde, Veldhoven

Background: There is an increasing societal demand for quality assurance and transparency of medical care. The National Academy of Medicine has determined patient-centeredness as a quality domain for improvement of health care. While many of the current quality indicators are disease-specific, most Emergency Department (ED) patients present with undifferentiated complaints. Therefore, there is a need for generic outcome measures. Our objective was to determine relevant Patient Reported Outcomes (PROs) for quality measurement of acute care.

Methods: We conducted semi-structured interviews in patients ≥ 18 years presenting at the ED for internal medicine. Patients with a cognitive impairment or language barrier were excluded. Physicians and nurses involved in acute care were also interviewed to identify differences in perspective between healthcare professionals and patients. Interviews were analysed using a coding framework.

Results: Thirty patients and ten professionals were interviewed. Patients and professionals reported outcomes as relevant in four domains: relief of symptoms, understanding the diagnosis, presence and understanding of the diagnostic and/or therapeutic plan and reassurance.

Conclusion: We determined four domains of relevant PROs for acute care in patients presenting for internal medicine. These domains will be used for developing generic Patient Reported Outcomes Measures for acute medical care. The patients’ perspective will be incorporated in these outcome measures with the ultimate aim of organising truly patient-centred care at the ED.
Rare adverse event: gastro-intestinal bleeding caused by deposition of sevelamer crystals

T.S. Schoot, T.E.H. Römkens, E.K. Hoogeveen
Jeroen Bosch Ziekenhuis, Afdeling Nefrologie, ’s-Hertogenbosch

Case: A 67-year old female with chronic renal failure stage G3bA3 with an eGFR of 32 ml/min/1.73 m² due to vascular disease and diabetes mellitus type 2 was admitted to the hospital with acute-on-chronic renal insufficiency due to decompensated aortic valve stenosis. Treatment with the oral phosphate binder sevelamer (total daily dose: 4 gram) was started because of a high serum phosphate of 2.0 mmol/l (reference range: 0.8-1.5 mmol/l) and later increased to 6.4 gram per day as serum phosphate concentration rose to 3.0 mmol/l. Five days after onset of sevelamer, rectal bleeding started and serum haemoglobin decreased from 5.9 mmol/l to 5.0 mmol/l (reference range: 7.5-10.0 mmol/l). A sigmoidoscopy was performed and revealed multiple deep ulcers (diameter 10-15 mm) and diffuse oedematous mucosa in the rectum. Pathologic examination showed deposition of sevelamer crystals in the ulcers without dysplasia, malignancy or chronic inflammation.

Diagnosis: Rectal bleeding owing to deep rectal ulcerations caused by deposition of sevelamer crystals.

Management: After discontinuing sevelamer, rectal bleeding gradually diminished.

Clinical relevance: Phosphate binders such as sevelamer are widely used in patients with chronic kidney disease. Mucosal ulceration induced by sevelamer crystals is a rare complication and should be considered in all patients using sevelamer presenting with gastro-intestinal symptoms, especially rectal bleeding. When sevelamer is ceased, symptoms are reversible and further mucosal damage is limited. As this side effect of sevelamer was not yet listed in the Dutch ‘Farmacotherapeutisch kompas’, it was reported to Lareb (the Dutch complication registry).
Abscopal effect of nivolumab in Hodgkin Lymphoma

E.M.J. Lammers¹, A. Claes², H.R. Koene¹

¹St. Antonius ziekenhuis, Afdeling Hematologie, Nieuwegein, ²UMCU, Afdeling Radiotherapie, Utrecht

Case: A 41-year old male patient was treated for hodgkin lymphoma (stage II, bulky disease). Treatment with standard chemotherapy did not result in persistent remission, nor did subsequent therapy with intensive chemotherapy followed by autologous stem cell transplantation and treatment with brentuximab-vedotin. Complete remission was eventually obtained on treating him with checkpoint inhibitor nivolumab. After 1-year of biweekly infusions with nivolumab, he complained of retrosternal pain and fatigue. PET-CT showed a relapse with several pulmonary active lesions in both lungs, with the most prominent lesions in the upper lobe of the right lung. Patient was treated with radiotherapy (10 fractions of 3 Gray), only on the largest lesions in the right lung. A PET-CT 5 weeks after the last radiotherapy treatment showed a complete metabolic response of all lesions. At present, this status of complete remission persists for 6 months.

Discussion: Abscopal effects are defined as tumor regression distal to the site of irradiation and were described in only a few earlier cases of hodgkin lymphoma. In refractory hodgkin lymphoma PD-L1 inhibitors such as nivolumab demonstrate a 70% response rate, however complete remissions are only seen in 20% of patients. Combining immunotherapy and radiotherapy has shown to improve progression free survival. One possible explanation for abscopal effects is that radiotherapy causes expression or release of tumor antigens during cancer cell death and thereby promote pro-inflammatory signals that trigger tumor-specific T-cells. Further research is required to determine optimal dosing and treatment schedules.
Body Weight Course in the DIAbetes and LifEstyle Cohort Twente (DIALECT-1) - a 20-year observational study

C.M. Gant1, I. Mensink2, S.H. Binnenmars3, J.A.M. van der Palen4, S.J.L. Bakker3, G.J. Navis3, G.D. Laverman4

1Meander Medisch Centrum, Afdeling Interne Geneeskunde, Amersfoort, 2Ziekenhuisgroep Twente, Afdeling Interne Geneeskunde, Almelo, 3Universitair Medisch Centrum Groningen/Universiteit van Groningen, Afdeling Nefrologie/Interne Geneeskunde, Groningen, 4Universiteit van Twente en Medical School Twente, Research Methodology, Measurement, and Data-Analysis, Faculty of Behavioral, Man, Enschede

Background: Although weight gain increases risk of type 2 diabetes, real-life data on the weight course in patients with established type 2 diabetes are scarce. We assessed weight course in a real-life diabetes care setting and analyzed its association with patient characteristics, lifestyle habits and initiation of insulin, glucagon like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i).

Methods: Data on weight, insulin, GLP-1 RA and SGLT-2i use were collected retrospectively (12 years) and prospectively (8 years) from patients included in the DIAbetes and LifEstyle Cohort Twente-1 (DIALECT-1, n = 450, age 61 ± 9 years, 58% men, diabetes duration [7-18] years). Lifestyle habits were assessed using validated questionnaires. The association of clinical parameters with body mass index (BMI) course was determined using linear mixed models. Patients who underwent bariatric surgery (n = 19) had a distinct BMI course and were excluded from the study.

Results: Baseline BMI was 31.3 (0.3) and was higher in women, patients aged < 60 years and patients with unfavorable lifestyle habits. BMI increased to 32.5 (0.3) after 12 years (P < 0.001), and decreased to 31.5 (0.3) after 20 years (P = 0.96, compared to baseline). Clinical parameters or initiation of insulin or SGLT-2i were not associated with BMI course. Patients who initiated GLP-1 RA declined in BMI compared to non-users (Pinteraction=0.003).

Conclusions: High BMI that real-life patients with type 2 diabetes gained earlier in life, remained stable in the following decades. Weight loss interventions should remain a priority, and GLP-1 RA might be considered to support weight loss.
Case: In June 2018, 20 patients visited our emergency department with complaints of nausea, malaise, headache, flushing, palpitations and dizziness. Patients presented themselves within a time frame of four hours. All patients worked in our hospital and had lunch in the hospital restaurant that day. After the second patient, food poisoning was suspected. An enquiry among patients identified a relation with the consumption of tuna. Based on the clinical presentation scombroid poisoning was suspected and all patients received supportive care with anti-histamines and complaints resolved without complications. The outbreak was reported to the Municipal Health Services.

Relevance: Fast recognition of scombroid poisoning can prevent new cases and reduce distress among patients, limiting unnecessary treatment and the use of diagnostic utilities. Source localisation can prevent further outbreaks of the same batch in other restaurants as well. Incidences of scombroid outbreaks in the Netherlands are scarce and often not reported. Therefore we describe a recent large outbreak of scombroid in the restaurant of our hospital.

Background: Scombroid poisoning results after consumption of toxic histamine levels in fish, notably tuna and mackerel. The process of histidine transformation into histamine concurs with bacterial overgrowth following inadequate temperature control. Symptoms usually arise after 10 till 20 minutes after consumption and are usually self-limiting in 24 hours. There is no clinical difference between endogenous histamine release in type-1 allergies and histamine poisoning. Diagnostic tests for differentiating between scombroid and allergies are not necessary since scombroid usually presents itself in a mass outbreak.
Hospitalisation of adult influenza patients costs the Dutch healthcare system annually 28 million euros

S.D. Marbus¹, V.A. Schweitzer², G.H. Groeneveld¹, J.J. Oosterheert¹, P.M. Schneeberger³, W. van der Hoek¹, J.T. van Dissel¹, A.R. van Gageldonk-Lafeber¹, M.J. Mangen¹

¹RIVM, Centrum Epidemiologie en Surveillance van Infectieziekten, Bilthoven, ²Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde, Julius Centrum, Utrecht, ³Leiden Universitair Medisch Centrum, Afdeling Infectieziekten, Leiden, ⁴Universitair Medisch Centrum Utrecht, Afdeling Interne Geneeskunde en infectieziekten, Utrecht, ⁵Jeroen Bosch Ziekenhuis, Regionaal Laboratorium voor Medische Microbiologie en Infectiepreventie, ’s-Hertogenbosch

Background: Influenza virus infections cause a high disease and economic burden during seasonal epidemics. However, there is still a need for reliable disease burden estimates to provide a more detailed picture of the impact of influenza. Therefore, the aim of this study is to estimate the incidence of hospitalisation for influenza virus infection and associated hospitalisation costs in adult patients in the Netherlands during one influenza season.

Methods: We conducted a retrospective study in adult patients with a laboratory-confirmed influenza virus infection in three Dutch hospitals during respiratory season 2014-2015. Incidence was calculated as the weekly number of hospitalised influenza patients divided by the total population in the catchment populations of the three hospitals. Arithmetic mean hospitalisation costs per patient were estimated and included costs for emergency department consultation, diagnostics, general ward and/or intensive care unit admission, isolation, antibiotic- and/or antiviral treatment. These hospitalisation costs were extrapolated to national level and expressed in 2017 euros.

Results: The study population consisted of 249 hospitalised adult influenza patients. The seasonal cumulative incidence was 3.5 cases per 10,000 persons in respiratory season 2014-2015. The arithmetic mean hospitalisation cost per influenza patient was €6,128 per patient in 2014-2015, resulting in total hospitalisation costs of €28 million in 2014-2015.

Conclusion: For the first time, we provide seasonal cumulative incidence of adult hospitalised influenza patients in the Netherlands. Hospitalisation costs of adult influenza patients, estimated at 28 million euros annually, constitute a considerable economic burden for the Dutch healthcare system.
Prediction of 30-day mortality in older medical emergency department patients

N. Zelis, J. Buijs, P.W. de Leeuw, S.M.J. van Kuijk, P.M. Stassen

1Zuyderland Medical Centre, Department of Internal Medicine, Heerlen,
2Zuyderland MC, Department of Internal Medicine, Heerlen, 3Maastricht University
Medical Centre+, Department of Internal Medicine, Maastricht

Background: Currently, adequate clinical models that predict 30-day mortality in older emergency department (ED) patients are lacking.

Methods: We performed a prospective multicentre cohort study to develop a prediction model for 30-day mortality in older (≥ 65 years) medical ED patients. Candidate predictors had to be objectively and reliably retrievable and widely available at an ED. We developed the model using logistic regression analyses. After internal validation, the model was externally validated in a separate cohort.

Results: The 603 patients in the derivation cohort had a median age of 79 years (IQR 73-85) and 51.6% were male. In the validation cohort, the median age of the 792 patients was 78 years (IQR 72-85) and 48.7% were male. Within 30 days after presentation, 66 (10.9%) patients in the derivation cohort and 105 (13.3%) patients in the validation cohort died. The model developed to predict 30-day mortality included the following 6 predictors: age, ≥ 2 abnormal vital signs, the serum concentrations of albumin, blood urea nitrogen and lactate dehydrogenase, and a bilirubin level >20 µmol/L. The AUC was 0.84 (95% CI: 0.78-0.89) in the derivation cohort and 0.83 (95% CI: 0.78 -0.87) in the validation cohort. The final model showed excellent calibration of observed and predicted risks.

Conclusion: We developed and externally validated an accurate and easy to use prediction model for 30-day mortality in older ED patients. Our model may contribute to fast recognition of patients at high risk of short-term mortality and to personalisation of diagnostics, treatment and care for older patients.
An unusual case of panhypopituitarism

E. Boele, J.M. Mekenkamp, M.J.M. Pouwels
Medisch Spectrum Twente, Afdeling Interne Geneeskunde, Enschede

Case: A 68-year-old man presented with complaints of fatigue, weight loss and muscle sore- and weakness. He had a 6-year long history of IgG-4 related pancreatitis, which at presentation had been in remission for a year with the use of mycofenolate mofetil. His symptoms had gradually developed in a year. Physical examination showed proximal muscle weakness. Laboratory testing showed panhypopituitarism with morning cortisol 24 nmol/l, TSH 0.54 mU/l, FT4 6 pmol/l and testosterone < 0.69 nmol/L. Prolactin was mildly elevated at 888 U/l. Magnetic resonance imaging revealed a slightly enlarged pituitary with obviously thickened pituitary stalk, consistent with hypophysitis. There were no signs of pituitary adenoma. Given his history of IgG-4 related pancreatitis, he was diagnosed with IgG-4 related hypophysitis. Upon diagnosis of the panhypopituitarism the patient immediately started hydrocortisone, and subsequently started suppletion of the other pituitary hormones including desmopressin. High dose steroids were withheld under the assumption that the long history of disease had already destroyed the pituitary beyond repair. The patient's symptoms resolved promptly and completely after starting hydrocortisone.

Conclusion: IgG-4 related disease is an immune-mediated disease that can affect a variety of organs such as the pancreas, bile ducts, thyroid, lungs and kidneys. IgG-4 related disease is increasingly found as cause of hypophysitis. It is treated with hormone replacement therapy and steroids. In some cases, this pathological condition can be refractory to medical therapy or recur after treatment, and can be life-threatening.
Upper leg amputation as treatment for pulmonary oedema in a patient with autonomic dysreflexia

A.H.A. Lavell, H.J. Voerman

Amstelland Ziekenhuis, Afdeling Interne Geneeskunde, Amstelveen

Case: We present a 68 year old male with diabetes mellitus type 2 and quadriparesis due to multiple sclerosis, who was admitted to the surgery ward with two necrotic ulcers on the lower left leg. Wound care was applied and intravenous flucloxacillin was administered. During admission the patient suffered from several episodes of severe hypertension (with systolic blood pressures up to 270 mmHg) combined with dyspnoea and higher oxygen demands. He was transferred to the intensive care unit with pulmonary congestion resulting in respiratory insufficiency, which recurred multiple times. Troponin levels were moderately elevated and cardiac ultrasound showed mild diastolic dysfunction without signs of systolic dysfunction or ischaemia. In the absence of a cardiac cause and after exclusion of a pheochromocytoma, the diagnosis of autonomic dysreflexia was made. An amputation of the upper left leg was performed. Postoperative no more episodes of hypertensive crises or pulmonary oedema were observed.

Discussion: Autonomic dysreflexia is a medical emergency that typically occurs in patients with spinal cord injury above T6, but has been mentioned in other neurological illnesses like MS. The syndrome is characterised by episodic hypertension, sometimes combined with baroreceptor induced reflex bradycardia. Noxious stimuli below the lesion, in our case leg ulcers, can induce an unmodulated sympathetic activation with massive vasoconstriction and lack of descending inhibition. This may lead to hypertensive emergencies and can be life threatening. Awareness among medical staff is essential to achieve early recognition and treatment by removal of provoking stimuli.
A rare cause of hemorrhagic diathesis

M.G.M. Kok, S. Oost
ZGT, Afdeling Interne Geneeskunde, Almelo

A 52-year old male patient with no serious antecedent illness presented at the emergency department with hemorrhagic diathesis, consisting of epistaxis for five days and painless hematuria since the morning of presentation. He further reported symptoms of an upper respiratory tract infection during the past two weeks. On physical examination several hematomas were seen on the extremities. Laboratory testing revealed low inflammatory markers, but prolonged coagulation times, with PT (12.5-14.5 sec) being 31.7 seconds and an APTT (25-35 sec) of 66 seconds. Fibrinogen (2-4 g/l) was 6.3 g/l. Mixing studies were obtained; both PT and APTT corrected incompletely indicating the presence of an inhibitor. Eventually, he turned out to have a factor X activity of 16%. The patient was referred to a tertiary center for further evaluation. Viral diagnostics did not yield any answers. PET-CT scanning revealed FDG positive lymphadenopathy mediastinal and supraclavicular. Multiple biopsies were performed, showing nothing more than reactive lymphoid tissue, consistent with infection.

The patient was treated multiple times with prothrombine complex, with temporary normalisation of FX activity, indicating a mild inhibitor. During follow-up factor X activity and coagulation times eventually normalised.

An acquired factor X inhibitor is a rare cause of hemorrhagic diathesis. The extensiveness of the coagulation defect is variable and could even be fatal. Few cases that have been described occurred following viral prodromes, or in association with malignancy. There is no consensus on treatment, but as in this case it could also be self-limiting.
Case: An 81 male and 83-year-old female couple presented to the emergency department with complaints of 3 days severe nausea, vomiting and diarrhoea after accidentally eating digitalis purpurea from their garden. At physical examination there were no signs of dehydration, blood pressure and pulse were normal. Blood results showed for the male and female respectively an eGFR 34 and 83 (normal value > 52 ml/min/1.7 m²), troponin T 295 and 45 ng/L (normal value < 34 ng/L) and normal electrolytes. The ECG was similar with ST depression in all leads and ST elevation in aVR. The digoxin levels were respectively 3.6 and 2.8 ng/mL (therapeutic levels 0.5-2 ng/mL). After consultation of the pharmacist, it was decided to admit both patients for cardiac monitoring without administering digoxin-specific antibody fragments (Digifab®). During admission the male patient showed severe arrhythmias including torsades des points, sinus arrest and 2nd degree AV block. All terminated spontaneously. It was found that digitalis purpurea not only consists of digoxin but also digitoxin, which has a longer biological half-life (7 days instead of 1.5 days) and is not incorporated in digoxin levels measured in blood. After 10 days both patients were discharged after normalization of their ECG.

Discussion: This case highlights that in patients with severe symptoms of digitalis purpurea intoxication, low-threshold administration of Digifab® should be considered even if digoxin levels in the blood are. In this consideration it is important to realize that digitalis purpurea consists of digoxin and digitoxin with different pharmacokinetics.
Psychosis due to polycythemia vera

H.S. De Lil, C.J.P.W. Keijsers, A.H.E. Herbers
Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, ‘s-Hertogenbosch

Case: An 86-year-old lady was admitted to the geriatric ward because of subacute psychotic derangement, variable aphasia, apraxia and right sided hemiballism. Physical examination including thorough neurological check-up revealed no further abnormalities. Laboratory work-up showed a haemoglobin of 10.0 mmol/l, hematocrite of 0.49 l/l, thrombocytes of 605x10^9/l and leucocytes of 12.9x10^9/l. No cause for a possible delirium was identified. Liquor investigation showed no signs of infection. A cerebral MRI-scan revealed no infarction or bleeding. After exclusion of rare causes of subacute neuropsychiatric decline such as limbic encephalitis, the consulted neurologist concluded that atypical Alzheimer’s disease or corticobasal degeneration could be the cause. During admission, because of persistent pancytosis a primary haematological condition was considered. The erythropoetin level was low and JAK2 mutation was present in the peripheral blood, compatible with a myeloproliferative disorder with preference for polycythemia vera. Phlebotomy was performed, whereafter not only hematocrite but also neuropsychiatric symptoms normalized within two days. We started carbasalate calcium and periodic phlebotomies. At first no chemical cytoreduction with hydroxycarbamide was commenced because of possible neuropsychiatric side-effects. The patient was discharged in stable condition and was able to resume her independent living situation. A few weeks after discharge we prescribed hydroxycarbamide. No neuropsychiatric symptoms reoccurred.

Discussion: Whereas cerebral infarction, headache and visual disturbances are a well-known complication of polycythemia vera, hemiballism and neuropsychiatric disturbances are a rare but incapacitating consequence. It is important to consider the diagnosis of a myeloproliferative disorder in case of persistent (pan)cytosis. Symptoms can often be reversed with phlebotomy.
Recurrent abdominal catastrophe, hypertension and renal failure apparent following resection of a pituitary adenoma

W.R. Berger, J.O. Groeneveld, C.W.H. de Fijter, Y.F.C. Smets
OLVG locatie Oost, Afdeling Interne Geneeskunde, Amsterdam

Case: Following resection of an ACTH-secreting pituitary adenoma, a 29 year-old man was frequently admitted to the hospital because of chronic abdominal pain and nausea, which was initially interpreted as a side-effect of cannabis/opiates. After another episode of severe abdominal pain, cholecystitis was suspected and laparoscopic cholecystectomy was performed (necrotic tissue). However, severe abdominal pain continued and he developed recurrent episodes of melena and haematemesis, with unremarkable gastroscopy or coloscopy. Furthermore, he developed frank hypertension and progressive renal failure, without postrenal obstruction or renal artery stenosis. As computed-tomography (CT) imaging of the abdomen and positron emission tomography (PET)-CT were not conclusive, diagnostic angiography was performed, showing extensive splanchnic microaneurysms. These findings were in accordance with a diagnosis of polyarteritis nodosa (PAN). Hepatitis B virus (HBV) test was positive and he was treated with a HBV nucleoside reverse-transcriptase inhibitor. The patient received surgical treatments of multiple intestinal perforations and aggressive medical treatment with corticoids and cyclophosphamide during hemodialysis.

Discussion: PAN is a systemic vasculitis that can virtually affect any organ. Patients typically present with systemic symptoms. HBV has been considered among the etiologic agents of PAN in 36% of cases. Treatment of HBV-PAN should aim at the suppression of HBV replication, combined with corticoids and cyclophosphamide. Plasma exchange may clear immune-complexes. The prognosis in patients with gastro-intestinal complications is very poor.
Severe systemic disease explained by the versatile role of interleukin-6, so time to switch it off

R. Tobal, J.P. Aendeker, J. Potjewijd, P. van Paassen
MUMC+, Department of Nephrology and Clinical Immunology, Maastricht

Dysregulated continuous synthesis of interleukin 6 (IL-6) induces formation of acute phase proteins by the liver together with pleiotropic activating effects on bone-marrow, and both the innate and acquired immune response. In the present case we postulate that uncontrolled IL-6 is the key interlinking factor causing a non-reported systemic disease, featured by life threatening cardiopulmonary, renal and gastrointestinal involvement.

A 72-year old woman with history of unclassified polyarthralgias presented with severe dyspnoea (6-minute-walking distance 50 meter, NYHA-IV), and long standing non-bloody diarrhea. Blood pressure was low and there were signs of right heart failure, without ischemia. Laboratory results indicated inflammation (high CRP, thrombocytosis), proteinuric renal insufficiency (s-creatinine 268umol/l, u-prot 2.1 g/l), and low albumin. Immune-serology was negative. There was no proof of infection. Echocardiography and right-heart catheterization (RCA) showed severe pre-capillary pulmonary arterial hypertension (WHO group 1), prompting immediate endothelin-blockade and PDE5-inhibition. Both kidney- and rectosigmoidal biopsy showed AA amyloidosis, which was absent in cardiac and pulmonary tissue. IL-6 is a well known trigger for AA-amyloidosis, and recent observations suggest that IL-6 signaling, and abundant production of IL-6 by pulmonary arterial smooth muscle cells, induces pulmonary vessel wall deformation and increased pressure. We therefore added tocilizumab (recombinant humanized mIgGκ-a-IL6-receptor). After 6-months follow-up repeat RCA showed impressive lowering of pulmonary arterial pressure. She was now NYHA-II, and kidney function and proteinuria improved, whereas her stool normalized.

Conclusion: Our unique case supports the crucial link between IL-6 and organ pathology, however along different pathways, in line with its pleiotropic biological effects.
Palmar fasciitis and polyarthritis syndrome: a rare paraneoplastic syndrome in patients with prostate carcinoma

A.G. de Boer¹, H.J. Bloemendal², R. Klaasen², M.C. van der Goes³

¹Meander Medisch Centrum, Afdeling Interne Geneeskunde, Amersfoort, ²Meander medisch centrum, Afdeling Interne Geneeskunde, Amersfoort, ³UMC Utrecht, Afdeling Reumatologie, Utrecht

Case: A 73 year old patient was seen in our hospital for treatment of metastatic adenocarcinoma of the prostate (pT1aN0M1a R0, BRCA-2 gene mutation). Prostatectomy and regional radiotherapy were performed and gosereline had been started because of disease progression. Because of castration resistant progressive disease enzalutamide was added. A decline of the PSA level was achieved. Before the start of enzalutamide, patient developed bilateral pain and stiffness of both hands combined with thickening of the hands. The symptoms progressed rapidly to bilateral flexion and extension contractures. The patient became unable to tie his shoelaces and had to use adjusted cutlery to eat. After consultation of the rheumatologist, additional X-ray, ultrasound and palmar skin biopsy of the hands were performed. The clinical picture resembles descriptions of “palmar fasciitis and polyarthritis syndrome” (PFPAS), a rare paraneoplastic syndrome. Positive effects of immunosuppressive medication have been reported in some cases. In our patient, treatment with oral prednisone (10 to 20 mg daily) showed no effect, therefore treatment was switched to methylprednisone pulses and methotrexate.

Conclusion: PFPAS is an uncommon paraneoplastic syndrome characterized by rapid onset of bilateral arthritis of the hands, fasciitis of the palms, progressive stiffness and contractures. The scarcity of knowledge about PFPAS makes it difficult to recognize it in an early stage. As a paraneoplastic syndrome, it has been linked to various malignancies. Thus far, PFPAS has been described in only two other cases of prostate cancer.
Incidence of cardiotoxicity over time in patients with HER2-positive metastatic breast cancer on long term treatment with trastuzumab and the potential risk factors

N.I. Bouwer¹, T.G. Steenbruggen², H.N. Rier¹, J.J.E.M. Kitzen¹, K.J. Beelen³, A.J. ten Tije⁴, P.C. de Jong⁵, J.C. Drooger⁶, C. Holterhues⁷, J.M. van Rosmalen⁸, M.J.M. Kofflard¹, E. Boersma⁸, G.S. Sonke², M.D. Levin¹, A. Jager⁸

¹Albert Schweitzer Hospital, Department of Internal Medicine, Dordrecht, ²Antoni van Leeuwenhoek, Department of Medical Oncology, Amsterdam, ³Reinier de Graaf, Department of Medical Oncology, Delft, ⁴Amphia Hospital, Department of Medical Oncology, Breda, ⁵Sint Antonius Hospital, Department of Medical Oncology, Utrecht, ⁶Ikazia Hospital, Department of Medical Oncology, Rotterdam, ⁷Haga Hospital, Department of Medical Oncology, Den Haag, ⁸Erasmus MC, Department of Biostatistics, Rotterdam

Background: Treatment with trastuzumab in some patients with HER2-positive metastatic breast cancer (MBC) can be prolonged for over ten years. Since trastuzumab can be cardiotoxic, the cardiac function should be monitored during trastuzumab treatment. However, guidelines for frequency and duration of cardiac monitoring during trastuzumab are unclear.

Methods: Patients with HER2-positive MBC treated with > 1 cycle trastuzumab in eight hospitals were eligible for the study. Data were collected through electronic medical records. We investigated two co-primary endpoints: 1) total cardiotoxicity defined as LVEF decline > 10%-points from baseline to LVEF < 50% and 2) severe cardiotoxicity defined as LVEF < 40%. Multivariable cox-regression and mixed model analyses were performed to identify risk factors.

Results: The cumulative incidence of total cardiotoxicity during follow-up was 22% (94 out of 429 patients) and of severe cardiotoxicity 6% (25 out of 429 patients). The incidence rate of cardiotoxicity and severe cardiotoxicity in the first year of trastuzumab was 11.7% and 2.6%. The incidence rate of total cardiotoxicity decreased the following years, while the incidence rate of severe cardiotoxicity was lower than the first year but remained stable over time. Smoking, low baseline LVEF (50-60%), cardiotoxicity during (neo)adjuvant treatment and cumulative anthracycline dose are independently associated with an increased risk of cardiotoxicity.

Conclusion: The incidence rate of total and severe cardiotoxicity peaks in the first year of trastuzumab treatment and decreases to a lower rate (< 5%) after four years of treatment. Therefore, cardiac monitoring in MBC patients seems most important in the first four years of trastuzumab treatment.
The association between the APOP screener and relevant clinical outcomes at different timepoints in older patients acutely hospitalized for internal medicine

L.C. Blommaard¹, J.A. Lucke¹, J. de Gelder¹, S. Anten¹, J. Alsm¹, S.C.E. Klein Nagelvoort Schuit¹, G.J. Blauw⁴, J. Gussekloo¹, B. de Groot¹, S.P. Mooijaart¹

¹Leiden University Medical Center, Department of Internal Medicine, section Geriatrics, Leide, ²Alrijne Hospital, Department of Internal Medicine, section Acute Care, Leiderdorp, ³Erasmus University Medical Center, Department of Internal Medicine, Rotterdam ⁴Haaglanden Medical Center, Department of Internal Medicine, Den Haag

Background: The recently developed and implemented APOP screener identifies older emergency department (ED) patients at high risk of mortality or functional decline after 3 months. The present study aims to explore the association between a high risk APOP result and various clinical outcomes at different timepoints in older patients acutely hospitalized for internal medicine, because this could have consequences for treatment decisions.

Methods: The Acutely Presenting Older Patient (APOP) study was an observational multi-center study in which patients aged ≥ 70 years were prospectively included at ED presentation and followed up 3 and 12 months after their ED visit. For this study, we included patients hospitalized for internal medicine. APOP screening was performed at ED presentation. Outcome measures were hospital length of stay (LOS), mortality and functional decline at 3 and 12 months.

Results: We included 323 patients with a median age of 80 (IQR 74-85) years of whom 94 (29%) patients had a high risk APOP screening result. The median hospital LOS in high-risk patients was 5 days (IQR 3-10) compared to 3 days (IQR 1-7) in low-risk patients, (p = 0.006). After 3 months, 27 (29%) of the 94 high risk patients had died and 29 (31%) experienced functional decline. After 12 months, 46 (49%) patients had died and 17 (18%) experienced functional decline.

Conclusion: The APOP screener identifies relevant clinical outcomes at different timepoints for acutely hospitalised internal medicine patients. Awareness of these outcomes could have consequences for treatment decisions or could be used in advance care planning.
Toxic Thyroid Nodules treated with Radiofrequency Ablation

H. de Boer, W. Bom, P. Veendrick, E. Bom, M. van Borren, F. Joosten
Rijnstate, Afdeling Interne Geneeskunde, Arnhem

Background: Toxic thyroid nodules are usually treated with radioactive iodine. This is associated with a high risk of permanent hypothyroidism. Radiofrequency ablation (RFA) may be a good alternative.

Patients and Methods: Twenty-one patients with a symptomatic toxic thyroid nodule, documented by suppressed TSH levels and a hot nodule on I-123 scan were treated with ultrasound-guided RFA, after local anesthesia, and in an outpatient setting. RFA was performed by the transisthmic approach. Follow-up was at least one year.

Results: All subjects had suppressed TSH levels, eight had mildly elevated FT4 levels, and five had a mildly elevated FT3. Four patients received antiarrhythmic treatment for chronic atrial fibrillation. RFA was not associated with clinically significant adverse effects. Euthyroidism was achieved in 11/21 patients (52%). A partial response with normalization of FT4 and FT3, and an incomplete improvement of TSH levels was observed in 6/21 patients (29%). Three patients had no response (14%), and one patient developed mild, but permanent hypothyroidism, that was treated successfully with levothyroxin 25 ug per day. Three patients underwent a second RFA treatment and this led to euthyroidism in all three, thereby raising the rate of complete remission to 67%. Recurrence of hyperthyroidism has not been observed so far.

Conclusion: These data suggest that radiofrequency ablation is a safe and promising treatment for symptomatic toxic thyroid nodules, with a low risk of permanent hypothyroidism. Current follow-up is too short to establish the recurrence risk of hyperthyroidism.
Implementation of a preoperative multidisciplinary team approach to improve outcome in frail elderly colorectal cancer patients

E. van der Vlies, P.G. Noordzij, A.B. Smits, M. van Hengel, H.P.A. van Dongen, M. Los
St. Antonius Ziekenhuis, Afdeling Inwendige ziekten, Nieuwegein

Background: The incidence of colorectal cancer (CRC) increases with age. Surgery is the main treatment for CRC but frail elderly patients are at increased risk for adverse outcomes. We aimed to determine if implementation of a preoperative multi-disciplinary team (MDT) approach for frail older surgical CRC patients improves postoperative outcome.

Methods: Historical cohort study from June 2015 - August 2018 in surgical patients aged ≥ 70 years with primary CRC. A comprehensive preoperative frailty screening was used to appraise the somatic, functional and psychosocial health status. A MDT weight the risk of surgery versus the expected gain in survival to guide preoperative decision making and initiate a tailored prehabilitation program. Primary endpoint was the occurrence of Clavien-Dindo Grade III-V postoperative complications. Secondary endpoints included length of stay, discharge destination and readmission. Rates of primary and secondary endpoints between patients with and without a MDT approach were compared.

Results: 378 patients were included in the study, 123 patients (32.5%) were referred for a MDT meeting (MDT patients). MDT patients were significant older, had higher rates of comorbidities and more frailty characteristics compared to non-MDT patients. The incidence of grade III-V postoperative complications was similar between MDT and non-MDT patients (13.6% (14/103) vs 8.6% (21/243), p = 0.539). No differences were present in secondary outcomes: length of stay (7 days vs 6 days, p = 0.475), discharge destination (home care or residential facility (58.2% (60/103) vs 35% (85/243)), p = 0.526) and readmission (14.6% (15/103) vs 8.6% (21/243), p = 0.084).

Conclusion: Implementation of a MDT approach for frail surgical patients with CRC results in comparable postoperative outcomes compared to non-frail patients.
A 35-year-old Turkish patient with a medical history of childhood tuberculosis and bacterial pleura empyema five years ago, was admitted with recurrent episodes of fever and abdominal lymphadenopathy. Repetitive lymph node extirpation showed an Epstein-Barr virus driven B-cell lymphoproliferative disorder with a detectable viral load. Treatment with rituximab resulted in reduction of B symptoms and lymphadenopathy for short-term. This medical history and the parental consanguinity prompted us to perform analyses on a primary combined immunodeficiency. A hitherto unknown homozygous mutation (c.551G > A) in the RAB27A gene, which encodes a guanosine triphosphate-binding protein of the Ras family, was found. RAB27A mutations drive the pathogenesis of the type 2 Griscelli syndrome, an autosomal recessive disorder characterized by immunodeficiency, hemophagocytic lymphohistiocytosis and hypopigmentation. Despite of the lack of hypopigmentation in our patient, his clinical course has been interpreted as fitting with Griscelli syndrome. The only curative treatment is allogenic bone-marrow transplantation. After diagnosis our patient was frequently readmitted to the hospital with neutropenic fever, hemophagocytic lymphohistiocytosis and progression of the lymphoproliferative disorder. Rituximab with combined chemotherapy was initiated in attempt to control the EBV driven lymphoproliferative disorder and to cure patient with allogenic bone-marrow transplantation. Unfortunately treatment failed and due to respiratory failure treatment was stopped. Consanguinity confers a higher risk of congenital abnormalities. The prevalence of consanguinity is up to ten percent worldwide with higher percentages in Northern-Africa and the Middle East. In daily practice deviant medical courses should urge us to consider congenital syndromes, especially in consanguineous patients.
Urea as second-line treatment for hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion: a case series involving 13 in-hospital patients

J. Woudstra, M. de Boer, E.N. van Roon, L. Hempenius
Medisch Centrum Leeuwarden, Department of Clinical Pharmacy and Pharmacology/Geriatrics, Leeuwarden

Background: Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) can pose a therapeutic challenge. After fluid restriction, urea is recommended as second-line treatment by the Dutch Practice Guideline ‘Het Acute Boekje’. Data on this practice are still scarce. We introduced urea for the treatment of SIADH in our hospital in December 2017 and prospectively collected data on its effectiveness and tolerability.

Methods: In patients with a serum sodium ≤ 129 mmol/L due to SIADH, urea in a dose of 0.25-0.50 g/kg was indicated if a prescribed fluid restriction had no effect or could not be applied. Measurement of serum sodium was performed at baseline, after the first (at 12-24 hours) and second (at 36-48 hours) gift of urea and at the end of in-hospital treatment. Statistical analysis included the Wilcoxon signed-rank test.

Results: Thirteen patients were treated with urea over a median of 5 days (range 2-10). Median serum sodium at baseline was 124 mmol/L (IQR 122-128) and increased to 128 (IQR 123-130) (P = 0.003) after the first; and to 130 mmol/L (IQR 127-133 mmol/L) (P = 0.002) after the second gift of urea. Normalisation of serum sodium (≥ 135 mmol/L) was seen in 8 (62%) patients. Seven (54%) patients reported intake difficulties due to the taste of urea. In one of these patients urea was discontinued because of co-reported nausea.

Conclusion: Our data show that urea, when tolerated, is an effective treatment strategy in hospitalized patients with SIADH.
A Complementary Complication

B.P. Jallah, S. Timmermans, J. Potjewijd, M.H. Busch, P. van Paassen
MUMC+, Afdeling Interne Geneeskunde, Maastricht

A 74-year-old female with thoracic and abdominal aortic aneurysm admitted for an elective (T)EVAR procedure postoperatively developed rapidly progressive acute kidney injury, Coombs negative hemolytic anemia, thrombocytopenia, paraplegia of the legs and purple/blue discoloration of the fingers and toes on day two. CT-cerebrum showed a lacunar infarct. Thrombotic thrombocytopenia purpura was considered and plasma exchange started. ADAMTS13 activity was normal and plasma exchanged was subsequently stopped. Sixteen days after the procedure systemic hemolysis persisted and the patient was dialysis dependent, so a kidney biopsy was performed. This showed lesions typical of acute Thrombotic microangiopathy (TMA). We simultaneously performed a novel in house ex vivo test which revealed endothelial restricted complement activation and C5b9 deposition. Atypical hemolytic uremic syndrome was diagnosed and eculizumab, a potent C5-blocker was started. Swift resolution of hematologic indices occurred and the patient was successfully weaned off dialysis. Genetics showed homozygous at risk haplotypes in the MCP/ggaac. We postulate that the endovascular procedure may have lowered the threshold for unrestrained complement activation and TMA to manifest. The favorable response to eculizumab and the functional ex vivo test underscores the key role of complement in mechanism of disease.

Acute kidney injury occurs in about 20% of patients after TEVAR with 4% permanently remaining dialysis dependent. Anemia and thrombocytopenia could also occur after endovascular surgery, this however is the first reported case of proven aHUS after TEVAR. Persistence of the above symptoms should trigger TMA analysis as timely intervention could lessen morbidity and mortality in this patient group.
Physical activity after eating: sometimes a shocking combination!

G.I.C.G. Ector, H.J. Jansen

Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, ’s-Hertogenbosch

Case: A 54-year old Caucasian male without relevant medical history was presented at the Emergency Department with signs of shock. He had been hiking when he experienced a generalized rash, itching and lightheadedness. Shortly afterwards, he collapsed with a brief loss of consciousness. He had no known allergies and his last meal 3 hours earlier consisted of peanut butter sandwich and pizza. Physical examination showed hypotension (RR 70/40 mmHg), generalized urticaria and no signs of dyspnea or angioedema. An anaphylactic shock was suspected and treated with epinephrine, clemastine and prednisone. The patient’s condition stabilized subsequently. Further anamnesis revealed this was his third episode. Since 1.5 year he experienced lightheadedness and hives while exercising. Three times this was accompanied by a loss of consciousness. He was referred to an allergist in order to investigate the cause of his anaphylactic reactions, by whom he was diagnosed with wheat-dependent exercise-induced anaphylaxis (WDEIA). He was advised to avoid ingestion of wheat-based food < 4 hours before exercising. Also, he should carry an emergency kit, including antihistamines, corticosteroids, and epinephrine, especially when exercising.

Discussion: Food-dependent exercise-induced anaphylaxis (FDEIA) is characterized by the onset of anaphylaxis during or soon after exercise, when preceded by the ingestion of a causal food allergen. FDEIA is divided into two types: in specific FDEIA, specific kinds of food cause anaphylaxis when exercise follows ingestion, but are tolerated if not followed by exercise. In non-specific FDEIA, those affected suffer from EIA after any meal followed by exercise, regardless of the food eaten.
Pitfalls of molecular diagnostic testing for Coxiella burnetii DNA on throat swabs

S.B. Buijs¹, M.H.A. Hermans², N. Agni², M. de Vries³, A.I.M. Hoepelman¹, J.J. Oosterheert¹, P.C. Wever¹
¹University Medical Center Utrecht, Department of Internal Medicine and Infectious Diseases, Utrecht,
²Jeroen Bosch Hospital, Department of Medical Microbiology and Infection Control, ‘s-Hertogenbosch,
³National Institute for Public Health and the Environment, Centre for Infectious Diseases Control, Bilthoven

Background: Coxiella burnetii, the causative pathogen of Q fever, is regularly detected in throat swabs from patients without subsequent serological evidence of Q fever infection and in bulk tank milk from dairy cows. We evaluated the value of polymerase chain reaction (PCR) for C. burnetii DNA on throat swabs and investigated whether recent consumption of C. burnetii-positive cow milk products could influence PCR test results.

Methods: C. burnetii PCR was performed on throat swabs obtained from: patients in whom a throat swab was ordered for non Q-fever related diagnostic purposes; patients with community-acquired pneumonia (CAP); and healthy volunteers after consumption of C. burnetii-containing cow milk products.

Results: C. burnetii DNA was found in 5% of throat swabs ordered for other diagnostic purposes and in 15.3% of CAP patients without serological evidence of Q fever pneumonia. The positive predictive value of C. burnetii PCR on throat swabs for the diagnosis of Q fever pneumonia was 66.7% (95% CI, 38.0-88.2). After consumption of C. burnetii-containing cow milk products, C. burnetii DNA could be detected in throat swabs for as long as 30 minutes after ingestion.

Conclusion: C. burnetii PCR on throat swabs is of low diagnostic value for Q fever pneumonia and was false positive in 15.3% of CAP patients without Q fever pneumonia. Recent consumption of C. burnetii-containing products can influence the outcome of C. burnetii PCR on throat swabs. Therefore, diagnosis of C. burnetii infection should be made in combination with serological results or PCR performed on serum.
High epidemic burden of RSV disease coinciding with genetic alterations causing amino acid substitutions in the RSV G-protein during the 2016/2017 season in the Netherlands

L.M. Vos¹, J.J. Oosterheert¹, S.D. Kuij², M.C. Viveen¹, L.J. Bont³, I.M. Hoepelman¹, F.E.J. Coenjaerts¹

¹UMC Utrecht, Afdeling Interne Geneeskunde/Infectieziekten, Utrecht, ²Amsterdam UMC – locatie AMC, Afdeling Medische Microbiologie, Amsterdam, ³WKZ Utrecht, Afdeling Kinderinfectiologie, Utrecht

Background: In 2016/2017 we had a severe epidemic respiratory syncytial virus (RSV) season in The Netherlands, which might be explained by genetic changes affecting virulence. We found genetic alterations in the G-glycoprotein of 2016/2017 RSV-A strains. We evaluated whether these mutations led to increased RSV incidence and disease burden.

Methods: We sequenced the G-glycoprotein of prospectively collected respiratory RSV strains from secondary care adult patients during the 2016/2017 and 2017/2018 epidemic RSV season. We evaluated associations between genetic, clinical and epidemiological data.

Results: We included 49 RSV strains; 28 2016/2017-strains (20 community acquired (CA) RSV-A, 5 hospital acquired RSV-A and 3 CA RSV-B) and 21 2017/2018-strains (8 CA RSV-A and 13 CA RSV-B). G-glycoproteins of 10 (50%) out of the 20 CA 2016/2017 RSV-A strains shared a set of eight novel amino acid mutations of which seven in mucin-like regions 1 and 2 and one in the heparin binding domain. This genetic variant was no longer detected among 2017/2018 RSV-A strains. Among patients carrying the novel RSV-A strain, 30% died.

Conclusion: An RSV-A strain characterized by the presence of eight mutations was found in 50% of the 2016/2017 CA RSV-A G-glycoproteins. Globally, this combination of mutations was never observed before. The appearance of this new strain characterized by the presence of 8 mutated amino acids coincided with an increased RSV peak in the Netherlands and was associated with higher disease severity. The transient character of this epidemic strain suggests rapid clearance of this lineage in our study community.
**Background**: Ethanol ablation (EA) for symptomatic thyroid cysts has produced highly variable and often disappointing results, probably because of differences in technical approach. Since January 2015 we employ a new, highly standardized, modified, ultrasound (US)-guided EA technique. The aim was to evaluate the one-year efficacy of a modified EA technique.

**Methods**: EA was performed in an outpatient setting, under US guidance, after local anesthesia, and by a trans-isthmic approach. After aspiration of cyst fluid, residual debris was removed by NaCl 0.9% irrigation, followed by instillation of ethanol 96%. After a retention time of 2 minutes, all ethanol was removed under US guidance. Then patients used their fingers for local pressure for 20 minutes. All patients with a 12-month follow-up were included for analysis. Successful treatment was defined as a cyst volume reduction of at least 75%, failure was defined as a reduction < 50%.

**Results**: Forty two patients have completed one-year follow-up. Median baseline cyst volumes was 18 ml (range 2.3-200 ml). Successful treatment was observed in 30/42 (71%) of patients, two patients had a partial response (50%-75%) and treatment failure occurred in ten patients (24%). Median cyst volumes decreased with a mean reduction of 92% (SD 1.9%) at 12 months (p < 0.001). Transient minor complications occurred in a small number of patients.

**Conclusion**: Modified EA produced a lasting volume reduction of at least 75% in nearly three quarters of patients, and was not associated with substantial side effects. It is recommended as a first line treatment, before considering surgery.
A 75-year old man was referred to our emergency department because of macroscopic hematuria and muscle weakness. His medical history revealed metastatic prostate cancer, initially treated with a LHRH agonist and 6 courses of upfront chemotherapy and in October 2017 after progression of disease enzalutamide was added to the hormonal treatment. At physical examination the patient was hypertensive and had bilateral lower extremity edema. Laboratory evaluation showed hypokalemia (2.7 mmol/l), metabolic alkalosis, elevated serum cortisol (1750 nmol/l), ACTH (40.4 pmol/l) and urine free cortisol (16000 nmol/24h). Abdominal CT scan showed lymphadenopathy and pelvic mass suspicious for progressive prostate cancer and enlarged adrenals. These results are compatible with the diagnosis of ACTH-dependent Cushing’s syndrome, caused by ectopic production. Pathology of a new prostate biopsy specimen showed a large cell neuroendocrine carcinoma (LCNEC) of the prostate. In addition a PET-CT scan with Ga-68-Edotreotide (DOTATOC) showed increased expression of somatostatin receptors in a subset of the bone metastases. Symptomatic treatment was started with potassium chloride, spironolactone, and ketoconazole as a cortisol synthesis blocking agent. No palliative chemotherapeutic therapy was initiated as his medical condition deteriorated and the patient died shortly after diagnosis.

To our knowledge, this is the first case of Cushing’s syndrome caused by ectopic ACTH production by a LCNEC of the prostate. These tumors can arise from conventional prostatic adenocarcinoma. Several studies suggest that long-term ADT produces a selective outgrowth of tumor cells with NE differentiation. Most of these neuroendocrine tumors are small cell carcinomas or carcinoids, LCNEC’s are extremely rare.
Alkaptonuria diagnosed in three siblings: Case report

K. Amaador, C.B. Hunting
St. Antonius ziekenhuis, Afdeling Interne Geneeskunde, Nieuwegein

Introduction: Alkaptonuria is an autosomal-recessive disorder caused by mutation in the homogentisate 1,2-dioxygenase (HGD) gene, leading to the inability to metabolize homogentisic acid (HGA) resulting in elevated levels in the blood. HGA is converted to a related substance forming polymers that are deposited as brown/black pigments in connective tissue, a process called ochronosis. HGA in the urine oxidizes and darkens the urine, the pathognomonic sign of AKU present at birth. Over time, ochronosis results in damage of cartilage primarily of weight-bearing joints causing osteoarthritis, the most prevalent disabling symptom in alkaptonuria.

Case: A 50-year-old male presented with joint pain in his left hip and was diagnosed with arthrosis. He underwent hip arthropathy during which ochronosis of his joint was noted. His history mentions dark urine since infancy and bluish discoloration of his ears. His sister presented with comparable complaints. Physical examination showed bilateral brown discoloration of the sclera and bluish discoloration of her auricles. Their younger brother complained about back stiffness and also had bluish discoloration of the ears. All three patients were diagnosed with alkaptonuria by urine testing which demonstrated strongly elevated HGA levels.

Conclusion: Although the symptoms of alkaptonuria are very characteristic and easily recognizable, it is a rare disease and underrecognized as diagnosis is often delayed until after the third decade. Alkaptonuria should especially be considered in patients with far more progressive athropathy than expected for their age. Nitisinone is a promising treatment of alkaptonuria. Early recognition and appropriate treatment are important to maintain quality of life.
The Haarlem study: a cohort of 100 male amateur athletes using anabolic androgenic steroids. Study design and baseline characteristics

D.L. Smit¹, O. de Hon², B.J. Venhuis¹, M. dHeijer¹, W. de Ronde⁴
¹Amsterdam UMC, locatie VUMc, Afdeling Interne Geneeskunde, Amsterdam, ²Dopingautoriteit, Afdeling ondersteuning, Capelle aan den IJssel, ³Rijksinstituut voor Volksgezondheid en Milieu, Centrum Gezondheidsbescherming, Bilthoven, ⁴Spaarne Gasthuis, Afdeling Interne Geneeskunde, Haarlem

Background: The use of anabolic androgenic steroids (AAS) is common among visitors of fitness centers. Knowledge about health risks of AAS use is limited due to lack of clinical studies.

Methods: We recruited 100 men, at least 18 years old, intending to start a cycle of AAS. Demographic data, reasons for AAS use, and historical AAS use were recorded at baseline. Subjects provided samples of AAS for analysis with UPLC-QTOF-MS/MS. Health analysis including blood, urine, and sperm analysis, electrocardiography and psychological questionnaires will be performed during 1 year follow-up.

Results: Baseline data were recorded for 111 men. 56% reported recent illicit drug use. If AAS were used before, 97% had experienced side effects. After exclusion, 100 men comprised the cohort for follow-up. The AAS cycle performed had a median duration of 13 weeks (range 2-52), median cost of €400 (range 50-5,600), and average dose of 901 mg per week (range 250-3,382). Subjects used other performance and image enhancing drugs (PIEDs), mainly growth hormone (21%) and clenbuterol (18%). 272 AAS samples were analyzed and 47% contained the AAS indicated on the label. Reasons for AAS use were diverse but mostly gain of muscle mass (44%). 48% self-reported to being addicted.

Conclusion: Strength athletes of the HAARLEM-study cohort use AAS and often also illicit drugs and other potentially harmful PIEDs. Quality of the AAS used is strikingly low. Follow-up of the cohort with repeated health analysis will provide novel data regarding health risks of AAS use.
Factors affecting emergency department length of stay for internal medicine patients

S. Vonk, S.U.C. Sankatsing, S.J.J. Logtenberg, J. Leermakers
Diakonessenhuis, Afdeling Interne Geneeskunde, Utrecht, Netherlands

Background: Emergency department length of stay (ED-LoS) is an increasingly discussed quality measure, as it has been linked to quality of care, patient safety and treatment outcomes. In this study we identified factors influencing ED-LoS for internal medicine patients and provided recommendations to shorten ED-LoS.

Methods: A retrospective cohort study was conducted at the emergency department (ED) of the Diakonessenhuis Utrecht in the Netherlands. Anonymised data for 7380 ED attendances, representing all internal medicine visits from January 2016 to January 2018 were analysed. Data included time of arrival and departure, sex, age, source of referral, triage category, destination, first visit and radiological examinations. With univariate analysis associations with ED-LoS were assessed. Furthermore, a survey was conducted among ED staff regarding factors influencing ED-LoS.

Results: The mean ED-LoS for all internal medicine patients was 220 minutes. Factors which significantly prolong ED-LoS were age (≥ 65 years), source of referral (with ambulance or own transport referred by the general practitioner), triage category (U2: emergent or U3: urgent), destination (admission), returning visit, radiological examinations done, season (winter or spring) and time of arrival (day or evening). The clinical staff rated bed occupancy rate in the clinic, consultations and diagnostics done as the most important factors influencing ED-LoS.

Conclusion: Several patient and circumstantial factors are associated with ED-LoS. Ways to shorten ED-LoS could be early contact with the clinical ward coordinator for patients ≥ 65 years who arrive by ambulance, creating time slots in the radiology programs, restructuring the morning report and creating an outpatient emergency clinic.
Roles and responsibilities of internists and Emergency Physicians at Dutch Emergency Departments: an explorative study

M.N.T. Kremers¹, J.J.H. Wachelder², P.W.B. Nanayakkara², H.R. Haak²

¹Maastricht University, Department of Health Services Research, and CAPHRI School for Public Health, Maastricht, ²Máxima Medisch Centrum, Afdeling Interne Geneeskunde

On behalf of the ORCA consortium

Background: The organization of the Emergency Department (ED) is gaining attention internationally, mainly due to an increased demand on Emergency Services influencing the quality of care negatively. In the Netherlands the organisational structure of EDs differs, probably influencing the care quality. However, detailed information about the various organisational structures of the EDs is lacking. This study aims to determine the organisational structure of the Dutch EDs. In addition, we aim to identify the role and responsibilities of internists and Emergency Physicians (EPs) for medical patients at the ED.

Methods: We performed a nationwide observational study. All hospitals with an ED in the Netherlands were identified in January 2018, contacted and surveyed. Requested information was retrieved from participating internists complemented by local administrative hospital data. Data were collected until January 2019.

Results: Sixty-five out of 92 EDs responded to the questionnaire (71%). Sixty (92%) EDs were 24/7 operational. A registered acute internist was present in 45 locations (69%) and EPs at 50 EDs (77%). EPs were 24/7 present at 25 EDs (38%). At 57 EDs (88%), medical residents treat medical patients. At 6 EDs an internist isn’t physically present (9%). Internists fulfil various roles at the ED, such as consultant, coordinator and manager. Collaboration between EPs and internists was graded with a mean of 7.3/10.

Conclusion: Our study shows that ED care is heterogeneously organised with different levels of involvement of internists in different settings. The influence of the role and presence of internists on quality of acute care, should be subject of future research.
A case of severe hypophosphatemia due to hyperventilation

F.D.P. van Bergen, I.N. Beaufort, W.J.M. Bos, A.J. Meinders
St. Antonius Ziekenhuis, Afdeling Interne Geneeskunde/MDL, Nieuwegein

Case: A 64-year old male with a medical history of asthmatic bronchitis presented on the emergency department with syncope, hyperventilation and aphasia after working in his crawlspace. He presented with a respiratory rate of 26/min and a saturation of 99% without oxygen therapy. His other vital parameters were in normal range. Normal breath sounds were heard during pulmonary auscultation. However, neurological symptoms were observed during physical examination, namely aphasia (E4M6V4) and generalized dysesthesia. Laboratory results showed a severe hypophosphatemia (0.14 mmol/L) and a high D-dimer (2466 µg/L). Arterial blood gas analysis showed a respiratory alkalosis with a pH of 7.69 with a bicarbonate of 17.0 mmol/L. CO poisoning was ruled out. CT cerebrum revealed no abnormalities and a pulmonary embolism was excluded with a thoracic CT.

Diagnosis: This patient was diagnosed with symptomatic severe hypophosphatemia due to hyperventilation. An exacerbation of his asthma caused hyperventilation, resulting in a decreased level of arterial CO2 and an extracellular shift of CO2. The resulting intracellular alkalosis causes phosphofructokinase stimulation and phosphate consumption. This leads to a shift of phosphate into the cell. Neurologic symptoms due to hypophosphatemia may be seen in phosphate levels ≤ 0.3 mmol/L.

Management: We administered 50mmol/12h phosphate intravenously. Serum phosphate level normalized to 0.87 mmol/L only two hours after presentation. This can be explained by normalisation of the respiratory rate. The aphasia resolved completely within these hours.

Clinical relevance: Hyperventilation can cause severe symptomatic hypophosphatemia due to respiratory alkalosis and is easily overlooked as a cause of neurologic symptoms.
Polycythemia caused by chronic carbon monoxide poisoning due to shisha (water pipe) use

N.J. Raaijmakers, J. Alsm
Erasmus medisch centrum, Afdeling Interne Geneeskunde, Rotterdam

Presentation: A 22 year old male was referred to our outpatient clinic by the dermatologist for evaluation of polycythemia. The patient visited the dermatologist because of facial plethora present since 4 years. Blood levels were last checked 5 years before and were normal at the time.

Investigations: During his initial visit he denied smoking cigarettes. Peripheral blood count revealed a hemoglobin level of 12.9 mmol/L and a hematocrit 60%. Erythropoietin level was 15.9 U/L. White blood count and differential were normal. The oxygen saturation was 99%. These findings suggested secondary erythrocytosis and subsequent analysis was performed; there were no clinical findings suggesting cardiopulmonary disease. A full body CT-scan showed no possible causes for secondary erythrocytosis. After these investigations we acquired an arterial blood gas, and found a Carbon Monoxide (CO)Hb of 21%.

Diagnosis: Patient still denied cigarette smoking but admitted to daily water pipe use. Despite the lack of symptoms we referred the patient to the emergency room for high flow oxygen treatment. The COHb dropped to 6%. The firedepartment investigated the patients house for CO levels but did not find it. We advised to discontinue shisha. After one month the hemoglobin level dropped to 11.9 mmol/L and EPO to 4.6 U/L.

Relevance: Waterpipe use is getting more common practice in the Netherlands and it is mainly used indoors. The consequences of an acute CO-intoxication due to waterpipe use are well known. However secondary erythrocytosis without other symptoms of CO-intoxication is rare. Only two other cases have been described before.
Bicytopenia and myelopathy caused by dietary copper deficiency

N.J. Raaijmakers, J. Alsma, J.L.C.M. van Saase
Erasmus medisch centrum, Afdeling Interne Geneeskunde, Rotterdam

Clinical presentation and clinical findings: A 52 year old man with no medical history was referred by the neurologist because of unintentional weight loss. The neurologist analyzed the patient because of a gnostic sensibility disorder and ataxia. At the time of his visit, he regained most of his weight, he contributed this weight loss due to a temporary loss of appetite.

Investigations: The blood results revealed a bicytopenia (hemoglobin level of 6.2 mmol/L and neutropenia 0.37 10^9/L). A CT-scan of the thorax and abdomen, and a bone marrow and kidney biopsy were obtained. The CT-scan showed no signs of malignancy, renal biopsy showed only mild chronic vascular and ischaemic disease. Bone marrow examination showed a striking vacuolization in the erythropoiesis and granulopoiesis. This was suspected for a toxic cause, alcohol abuse or a copper deficiency. The copper level in the blood was lower than 1.57 µmol/L, ceroluplasmin < 0.09 g/L and zinc 88.50 µmol/L.

Diagnosis and intervention: Copper deficiency is known to cause cytopenia and neurological symptoms. The differential diagnosis consists of decreased dietary intake of copper, decreased uptake due to gastric surgery, enteropathies, excessive zinc ingestion or aceruloplasminemia. We found no underlying disease in our patient, which makes the decreased dietary intake the most likely suspect. After oral copper supplementation the bicytopenia disappeared. The neurological symptoms are slowly improving.

Relevance: Copper deficiency is a rare, but is relatively easy to diagnose and treat. It should be included in the differential diagnosis in patients with myelopathy and cytopenia.
Funduscopy: yes or no? Hypertensive crisis and retinopathy in the emergency care setting; a retrospective cohort study

C.M. Nijskens¹, S.R. Veldkamp¹, D.J. Van der Werf², A.H. Boonstra¹, M. Ten Wolde⁴
¹Flevoziekenhuis, Afdeling Interne Geneeskunde, Almere, ²Flevohospital Almere, Afdeling Ophthalmology, Almere

Background: According to international guidelines patients admitted to the emergency department (ED) for hypertensive crisis (HC) should undergo comprehensive evaluation including funduscopic examination. Evidence for funduscopy in determining therapy and clinical course is weak and little is known about the prevalence of retinopathy in this setting. In order to characterize which patients should undergo funduscopy, we studied the prevalence, characteristics and clinical outcome in patients with HC and retinopathy grade III/IV.

Methods: We conducted a retrospective cohort study of consecutive patients with HC admitted to the ED between 2012 and 2015. Patients with a systolic blood pressure (SBP) ≥ 180 mmHg or diastolic blood pressure (DBP) ≥ 120 mmHg at time of presentation were included.

Results: A total of 271 patients were included, of whom 18 (6.6%; 95%CI 3.9-10.5) had hypertensive emergency. In 121 patients (44.6%; 95%CI 37.1-53.3) funduscopy was performed, of whom 17 (14.0%; 95%CI 8.2-22.5) had retinopathy grade III/IV. SBP and DBP were significantly higher in patients with retinopathy (p = 0.012, p = 0.043 respectively). However, retinopathy was also seen in patients with lower blood pressures (SBP < 200 mmHg and DBP < 120 mmHg). No differences in other clinical characteristics, including visual disturbances, were found. One patient with retinopathy developed ischemic stroke after taking oral medication.

Conclusion: Funduscopy is frequently omitted in patients presenting with HC. However, the prevalence of retinopathy grade III/IV is high among examined patients. No clinical signs or symptoms predict the presence of retinopathy grade III/IV. We therefore conclude that funduscopic examination should be performed in every patient with HC.
Evaluation of blood culture epidemiology and efficiency in a large European teaching hospital

R.S. Nannan Panday, N. Alam, P.W.B. Nanayakkara

Amsterdam UMC Location VU University Medical Center, Department of Internal Medicine, Section Acute Medicine, Amsterdam

Background: Blood cultures remain the gold standard for detecting bacteremia despite their limitations. The current practice of blood culture collection is still inefficient with low yields. Limited focus has been given to the association between timing of specimen collection at different time points during admission and their yield.

Methods: We analyzed 3,890 sets of cultures collected from 1,962 admitted patients over the seven-month period of this study. We compared blood culture yield between the early group (≤ 24 hours after admission) and late group (> 24 hours of admission). We also investigated the effect of prehospital oral antibiotics and pre-analytical time on the first cultures in the emergency department.

Results: In total, 3,349 (86.1%) blood cultures were negative and 541 (13.9%) were positive for one or more microorganisms. After correcting for contamination, the overall yield was 290 (7.5%). The early group (n = 1,490) yielded significantly more true-positive cultures (10.1% versus 5.8%, p < 0.001) than the late group (n = 2,400). The emergency department had a significantly higher yield than general wards, 11.2% versus 5.7% (p < 0.001). Prehospital oral antibiotic use and pre-analytical time did not affect the yield of first cultures at the emergency department (p = 0.735 and 0.816 respectively).

Conclusion: This study showed that blood cultures have a low yield. Cultures collected during 24 hours after admission yielded more positive results than those collected later. Future studies should aim at improving blood culture yield, implementing educational programs to reduce contamination and cost-effective application of modern molecular diagnostic technologies.
Severe hemolytic anemia due to transient acquired G6PD deficiency after ingestion of sodium chlorite

P.B.J.E. Hulshof, J. Veenstra
OLVG West, Afdeling Interne Geneeskunde, Amsterdam

Background: Sodium chlorite is a strong oxidant used as bleaching agent and household detergent. Ingesting sodium chlorite can lead to oxidative stress in red blood cells, causing methemoglobinemia and severe intravascular hemolysis that can lead to multi-organ failure. Only three cases have been described in literature. Transient acquired G6PD deficiency is hypothesized to be a key component in the pathophysiology of sodium chlorite intoxication.

Case details: A 40 year old female was presented to our emergency department after ingestion of an unknown amount of sodium chlorite solution. She developed methemoglobinemia and severe intravascular hemolysis. Transient decreased G6PD activity was observed. The patient was closely observed and received only supportive treatment. She recovered fully.

Discussion: Sodium chlorite intoxication is potentially life threatening because it can lead to severe intravascular hemolysis and multi-organ failure. The pathophysiological mechanisms are not fully understood, but an acquired transient G6PD deficiency appears to be a key component.
Synthetic cathinones among novel psychoactive substances: two patients with psychosis after chloromethcathinone use

K.S. van Wonderen, A.J. Meinders
St. Antonius Ziekenhuis, SEH, Nieuwegein

Case: Two 18-year old men of eastern European descent were brought into the emergency department by ambulance with unexplained abnormal behaviour. They admitted to having smoked cannabis with the possible addition of another substance 2.5 hours before presentation. Patient 1 is calm and cooperative in the ambulance and in the emergency department (ED). He does not resist examination in the ED. Patient 2 is very agitated during transport and is given midazolam intravenously. He is responsive but anxious in the ED and is given additional midazolam to facilitate examination. Both patients had normal vital signs with the exception of mild tachycardia (110-120/min) and normal size pupils unresponsive to light. Both developed urinary retention. ECG and blood tests were normal, including hemocytometry, renal function, liver enzymes, creatinine kinase and bicarbonate. Blood alcohol levels were negative.

They boarded in the ED and were eventually transferred to a medium care unit. During their stay they slept with occasional bouts of aggression and anxiety, occasionally requiring intravenous benzodiazepines. The consulting psychiatrist diagnosed both patients with psychosis due to withdrawal of unknown drugs of abuse. The symptoms started to subside spontaneously within 24-36 hours after presentation. They were discharged two days after admission.

Qualitative urinalysis using gas chromatography/mass spectrometry confirmed the presence of chloromethcathinone (CMC) also known as ‘clexphedrone’ in both patients.

Conclusion: The use of chloromethcathinone may lead to prolonged psychotic symptoms requiring supportive care. CMC is currently one of the five most confiscated synthetic cathinones in Europe.
Fatal error or game fix? Cognitive overload and learning potential of the serious game DiagnostiGo

Background: Recognising patients with infectious diseases and up-to-date knowledge on antimicrobial use requires repeated education. More patient exposure is usually not feasible in current curricula, therefore using a serious game may be beneficiary. However, serious games can induce cognitive overload: players need their attention to understand the game and are therefore prevented from learning by playing. We studied learning potential and cognitive overload of our game DiagnostiGo by testing knowledge increase after gameplay.

Methods: Physicians waiting for a regular antibiotics course were asked to participate. A 15-question pre-test was offered to all participants. After stratified randomisation, participants were allocated to either the control group or the intervention group. The control group continued patientcare as usual, the intervention group played a maximum of 5 virtual patient cases with DiagnostiGo additional to daily patientcare. After two weeks a 15-question post-test was offered.

Results: 44 participants took both pre-test and post-test (21 control group vs 23 game group). Mean increase in knowledge was -0.4 points in the control group vs +0.8 points in the game group (p = 0.053). Mean increase in knowledge if played > 1 Case: -0.4 vs +1.2 points (p= 0.03). Mean knowledge increased with the number of cases played: -4.0 (0 cases), -5.5 (1 case), +1.5 (3 cases), +2.0 (4 cases), +1.4 (5 cases).

Conclusion: By playing DiagnostiGo players increase their knowledge on infectious diseases and antimicrobial use. The more cases were played, the more knowledge was gained suggesting some degree of cognitive overload is present initially but rapidly decreases while playing.
Toxin-induced haemolysis secondary to Clostridium Perfringens

J.J. Engel, M. Egal, M. Berrevoets
Elisabeth-Tweestedenziekenhuis, Afdeling Interne Geneeskunde, Tilburg

Case: A 59-year-old woman with no relevant medical history presented to our emergency department with complaints of abdominal pain and icterus. History revealed unintended weight loss of 10 kilograms. She was tachycardic with a tender abdomen and muscular defence in the left lower quadrant. Serum creatinine (144 µmol/L), bilirubin (367 µmol/L) and C-reactive protein (320 mmol/L) were markedly elevated. Blood count showed anaemia (4.4 mmol/L), leucocytosis, mild thrombocytosis and reticulocytosis. Microscopic blood slide showed ghost red blood cells, consistent with intravascular haemolysis. Direct antiglobulin tests were negative. Imaging revealed a large, poorly definable intrapelvic mass containing air bubbles, with dilated pyelocaliceal systems due to bilateral ureteric compression. We started cefuroxime-metronidazole at admission on a clinical suspicion of haemolytic anaemia secondary to an infection with an underlying gynaecological or intestinal malignancy. Shortly after admission, the patient had a witnessed cardiac arrest due to ongoing haemolysis (haemoglobin 2.8 mmol/L). Cardiopulmonary resuscitation was successful and patient was transferred to the ICU. Unfortunately, she died from multi-organ failure two days later. Post-mortem biopsy of the mass showed a necrotising, poorly differentiated carcinoma with cultures positive for Clostridium perfringens, among other bacteria. Discussion: Clostridium perfringens is a Gram-positive, anaerobic, rod-shaped bacterium which produces alpha-toxin, a protein which can cause massive haemolysis and myonecrosis. In this case, the elevated CRP, absence of thrombocytopenia and the abdominal mass with intratumoral gas alluded to Clostridium perfringens as the underlying pathogen. Rapid recognition of a toxin-induced haemolysis due to C. perfringens and early intervention are critical for patient survival.
Health related Quality of Life in sepsis survivors

R.S. Nannan Panday, N. Alam, P.W.B. Nanayakkara, T.C. Minderhoud
Amsterdam UMC - Location VU University Medical Center, Department of Internal Medicine, Section Acute Medicine, Amsterdam

Background: Due to the rise in incidence, long term effects of sepsis are becoming more evident. There is increasing evidence that sepsis may result in impaired Health Related Quality of Life (HRQoL). The aim of this study was to investigate whether HRQoL is impaired in sepsis survivors and which clinical parameters are associated with the affected HRQoL.

Methods: In order to answer these questions we analyzed 880 Short Form 36 (SF-36) questionnaires that were sent to sepsis survivors who participated in the Prehospital Antibiotics Against Sepsis (PHANTASi) trial. These questionnaires were sent by email, 28 days after discharge.

Results: Data from the general Dutch population, was obtained from the Netherlands Cancer Institute (NKI-AVL) and served as a control group. Subsequently, 567 sepsis survivors were matched to 567 controls. We found that sepsis survivors have worse HRQoL compared to the general Dutch population. This negative effect was more evident for the physical component than the mental component of HRQoL. HRQoL was significantly altered by advancing age and female sex. We also found that hospital length of stay, comorbidity negatively affect the physical component of HRQoL.

Conclusion: In our study we found that HRQoL in sepsis survivors, 28 days after discharge, is severely diminished in comparison with the general Dutch population. The physical domain is more severely affected, whereas the mental domain is influenced less. Length of stay, comorbidity, advancing age and female sex all have a negative effect on the Physical Component Scale (PCS) of the HRQoL.
Severe sepsis or heroin intoxication?
The use of heroine metabolites in clinical practice; a case report

L. van Hoeven, C. Bethlehem, J. Alsma
Erasmus MC, Afdeling Interne Geneeskunde, Rotterdam

**Background:** There is an increasing incidence of heroin use and heroin-related overdose deaths. The verification of recent heroin abuse is challenging, as heroin itself can hardly be detected. The detection of different metabolic products of heroin or street heroin impurities can be a promising method.

**Case Presentation:** A 23-year-old man was brought to our ER because of out of hospital cardiac arrest. He was hemodynamic unstable, with Glasgow Coma Scale of 3 and temperature of 38.5°C. Blood tests were suggestive of renal failure, liver failure and metabolic acidosis with seriously elevated potassium. Notably, the inflammation parameters were not elevated. According to family there was no medical history and patient didn’t used medications or drugs. Chest radiographic showed pulmonary infiltration. Patient was admitted to ICU with a differential diagnosis of severe pneumosepsis with multiple organ failure, but also toxicology elevation for drugs abuse was taken. The toxicology report was positive for morphine, hydromorphone, codeine and papaverine, which is highly suggestive of recent heroin consumption. Patient deteriorated despite maximally therapy at the ICU and died. There was no permission for autopsy.

**Discussion:** It is not clear whether this patient has died of refractory sepsis or of heroin abuse, however this case report shows that toxicology screening in critically ill patients with an unclear presentation can be helpful in the differential diagnosis. In our hospital this was the first case with the detection of papaverine in combination with other metabolites of heroine, which can be a promising method to detect abuse of heroin.
Early worsening of diabetic retinopathy in a pregnant patient: an eye-opener

H.J. Jansen, K.P. Bouter, F. Rovers, K. Allali
Jeroen Bosch Hospital, General Internal Medicine, Den Bosch

A 30-years old patient with type 1 diabetes mellitus was recently seen and reported an unplanned pregnancy. At presentation glycated hemoglobin (HbA1c) equalled 8.3 mmol/mol. Patient was treated with basal-bolus insulin regimen. Insulin therapy was intensified and she received a continuous glucose monitoring system, for restoration euglycemia. After 4 weeks of intensified treatment, glucose levels returned normal considering HbA1c level of 5.4 mmol/mol. Blood pressure was normal. Due to vision complaints the ophthalmologist was consulted. Retinal examination showed severe non-proliferative diabetic retinopathy (DR) with macular edema on optical coherence tomography. Her previous examination in 2015 showed minimal DR. Careful monthly follow up showed evolvement to the proliferative form of DR with the prompt start of pan retinal photocoagulation. The clinical effect of laser therapy in our patient has to be determined. Diabetic retinopathy in pregnancy is considered a debilitating medical condition. Pregnancy is a risk factor for DR progression and is associated with increased DR prevalence. Factors associated with DR progression in pregnancy include diabetes duration, DR severity at conception, hyperglycaemic control, anaemia and coexisting hypertension.

Rapid implementation of tight glycaemic control has also been associated with worsening of retinopathy in pregnant women with type 1 diabetes. Guidelines recommend that pregnant women with pre-existing diabetes be offered retinal assessment by examination and fundus retinal imaging. In addition they suggest that DR should not be considered a contraindication to rapid glycaemic control in women with a high HbA1c in early pregnancy, but rather that retinal assessment is essential in such individuals.
Environmental co-exposure to cadmium and lead and the association with diabetic kidney disease; another reason to avoid smoking and alcohol intake in patients with T2DM?

I.J.M. Hagedoorn¹, S. van Huizen¹, C.M. Gant², R.G.H.J. Maatman¹, G.J. Navis³, S.J.L. Bakker³, G.D. Laverman³

¹ZGT, Department of Internal Medicine, Division of Nephrology, Almelo, ²Meander Medisch Centrum, Department of Internal Medicine, Amersfoort, ³University Medical Center Groningen, Department of Internal Medicine, Division of Nephrology, Groningen

Background: Environmental factors contributing to diabetic kidney disease (DKD) in type 2 diabetes mellitus (T2DM) are incompletely understood. We investigated whether blood concentrations of cadmium (Cd) and lead (Pb) were associated with prevalent DKD, and to which extent diet and smoking contribute to blood Cd and Pb concentrations.

Methods: We performed a cross-sectional analysis in 240 patients with T2DM included in the DIAbetes and LifEstyle Cohort Twente (DIALECT-1). Blood Cd and Pb concentrations were determined from EDTA whole blood samples. Cd-Pb co-exposure was calculated by addition of Cd and Pb Z-scores. The association between Cd-Pb and DKD (CKD-epi < 60 ml/min/1.73m² and/or albuminuria) was determined using multivariate logistic regression. The association between diet (derived from food frequency questionnaire), smoking and Cd and Pb was determined using multivariate linear regression.

Results: Almost half of all participants had DKD (49%). Median blood concentrations were 0.33 ug/l (IQR: 0.21-0.57 ug/l) for Cd and 1.45 ug/dl (IQR: 0.83-1.86 ug/dl) for Pb, all below the values known for acute toxicity. Higher Cd-Pb was associated with a 32% higher risk for DKD (OR: 1.317 (1.071-1.620), p = 0.009). Smoking status was positively associated with Cd (β: 0.479, p < 0.001) and alcohol intake with Pb (β: 0.299, p < 0.001), while there was no association between dietary intake and Cd or Pb.

Conclusion: The association between higher Cd-Pb and prevalent DKD might suggest Cd and Pb contribute to progressive DKD. The higher Cd-Pb associated with smoking and alcohol might provide another mechanism by which these intoxications adversely affect renal health in T2DM.
Learning Curve of Ultrasound-guided Radiofrequency Ablation for Symptomatic, Benign, Non-Toxic Thyroid Nodules

W.J. Bom, P.B. Veendrick, E.P. Bom, M.M.G.J. van Borren, R.R.J.P. van Eekeren, F.B.M. Joosten, J.M.M. de Boer
Rijnstate, Afdeling Radiologie, Arnhem

Background: Radiofrequency ablation (RFA) for symptomatic, benign thyroid nodules was started in Rijnstate Hospital in January 2015. So far, we have treated 110 subjects with non-toxic nodules. According to the current literature a mean nodule volume reduction of 80% should be achievable, in experienced hands. The aim was to evaluate the 6-month efficacy of RFA in reducing thyroid nodular volumes and nodule-related symptoms, and to assess the degree of experience required to meet the current international standard.

Methods: RFA was performed in an outpatient setting, under local anesthesia, using the moving shot technique and the transisthmic approach. All patients with a follow-up of at least 6 months after first RFA were included.

Results: To date, 65 patients have completed the 6 month follow-up. Nodule volume reduction was achieved in all but three patients. Mean volume reduction was 26% in the first ten patients, 52% in the second ten, 71% in fifth ten, etc. In most patients, a volume reduction of 30% was sufficient to experience a significant reduction in nodule-related symptoms. The achieved results indicate that at least 40 procedures are required to guarantee an individual volume reduction of 50% with high likelihood. The learning curve based on current results predicts that at least 125 procedures are needed to achieve a mean volume reduction of 80%

Conclusion: RFA is a highly effective, non-surgical, treatment in patients with symptomatic, benign thyroid nodules. However, substantial technical experience is required to achieve the international standard, defined as a mean volume reduction of 80%.
Warning: Energy overload! Locate the source and reduce power

C.I. van der Made, H.J. Jansen, K.P. Bouter
Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, ’s-Hertogenbosch

Case: A 43-year-old woman presented at the Emergency Department with distinct tremors and shaking of the hands and feet. Her medical history included Graves’ disease, for which she was treated with block-replace drug therapy in 2007. Physical examination revealed an anxious, tachycardic patient with pronounced shaking and postural tremors of the hands and feet. The calculated thyreotoxic crisis score was 50. Laboratory investigation confirmed our suspicion of a relapse of her Graves’ disease, with thyroid-stimulating hormone (TSH) levels below the reference value of 0.008 mU/L, with a free T4 level of 150 pmol/L (reference 12-23 pmol/L) and a T3 level higher than 30.80 pmol/L (reference 3.5-6.5 pmol/L). Immediate treatment was started with propylthiouracil, potassium iodide, hydrocortisone and propanolol. Upon the administration of the propanolol, the tremors markedly diminished within 30 minutes. After intensive drug treatment and subsequent total thyroidectomy, the patient completely recovered. She was discharged with levothyroxin.

Discussion: Our patient exhibited symptoms resulting from thyroid storm. This condition is extremely rare (0.20 in 100,000 patient years). It is caused by a hypermetabolic state with dramatic activation of the sympathetic nervous system and increased sensitivity to catecholamines. Precipitating factors include infection, trauma, diabetic ketoacidosis, surgery or abrupt discontinuation of antithyroid medicine. Clinical relevance: Thyroid storm is considered to be a medical emergency that warrants prompt intervention. Early recognition is therefore indispensable. This case describes a patient with thyroid storm who presented with anxiety and physiological postural tremors of the extremities as cardinal presenting symptoms.
Ultrasound-guided Core Needle Biopsy for Thyroid Nodules Improves Diagnostic Yield

A. van den Ende, H. de Boer, F. Joosten, H. Zandvoort
Rijnstate ziekenhuis, Afdeling Radiologie, Arnhem

Background: Fine needle aspiration (FNA) is standard practice for thyroid nodule evaluation. However, results may be non-diagnostic in up to 20-30% and false-negatives or false-positives occur 10%. The aim of our research is to examine the diagnostic yield of core needle biopsy (CNB) in patients with thyroid nodules requiring evaluation.


Results: Between 2015 and 2018, 85 patients underwent CNB of a thyroid nodule. Maximal nodule diameter ranged from 9 - 70 mm. Forty-one patients had a CNB because of FNA's with a B-I or B-III classification, and 44 because of a high clinical suspicion for malignancy, or persistent clinical diagnostic uncertainty. The first CNB was diagnostic in 81 patients (95.2%). Four patients required a second CNB because the amount or quality of the biopsy material was insufficient to establish a diagnosis. All but one of the second CNB’s were diagnostic. Four patients developed a small subcapsular hematoma, easily controlled by local pressure. Other complications were not observed.

Conclusion: Core needle biopsy of thyroid nodules, performed by experienced radiologists, is a safe procedure and is associated with a much higher diagnostic yield than FNA. We recommend CNB as a second line procedure if the first FNA is inconclusive. Primary CNB is recommended if clinical suspicion for primary or secondary cancer is high.
Nausea due to hypercalcemia?

T. Barneveld, E.E.M. van Ginneken, G.J. Scheffer-Nijsen, J.C. Kuenen
Gelre Ziekenhuizen, Afdeling Internal Medicine, Apeldoorn

Case: A 78-year old woman presented with complaints of nausea since six months. Her medical history mentioned endometrium carcinoma stage 1a grade 3 in 2000, hypertension and restless legs. Laboratory results showed elevated (ionized)calcium (1.41 and 2.94 mmol/L) and PTH (15 pmol/L) levels. Ultrasound and CholinePET-CT scan showed a parathyroid adenoma. With forced hydration and APD intravenous calcium level returned to normal. Ropinirol was discontinued but Megestrol (antihormonal therapy started 5 years ago because of local irresectable recurrence of endometrium carcinoma) was continued. Both can give side-effects of nausea. Patient was readmitted to the hospital because of dehydration and persistent nausea.

Diagnosis: An early morning cortisol level was low (0.08 umol/L) and an adrenal stimulation test showed inadequate results. Besides hyperparathyroidism, adrenal insufficiency due to Megestrol use, a well described side effect, was diagnosed. Megestrol is a synthetic progestin with antineoplastic and orexigenic properties. In addition to its effects on the progesterone receptor, Megestrol also binds to the glucocorticoid receptor. Some patients receiving Megestrol have been reported to develop clinical features of glucocorticoid excess, while others have experienced the clinical syndrome of cortisol deficiency -either following withdrawal of Megestrol therapy or during active treatment.

Management: Hydrocortison was prescribed, Megestrol discontinued, parathyroidectomy performed with priority and nausea disappeared.

Clinical relevance: Despite management and recovery of hypercalcemia, nausea persisted, due to the combination with adrenal insufficiency. When not diagnosed on time, adrenal insufficiency can be life threatening. Clinicians should be aware of the potential effects of Megestrol on the hypothalamic-pituitary-adrenal (HPA) axis.
Intracerebral haemorrhage as presenting symptom of Conn’s syndrome

C.A.J. van Beers, A.J. van Tienhoven, S.R. Niehe
OLVG West, Afdeling Interne Geneeskunde, Amsterdam

Case: A 61 year old female was admitted to the ICU with a hypertensive intracerebral haemorrhage. Blood tests showed a hypokalaemic metabolic acidosis (potassium 2.5 mmol/l; pH 7.46; bicarbonate 32.1 mmol/l). She was treated with intravenous labetalol and potassium. For adequate blood pressure control, she needed four types of oral antihypertensive drugs (amlodipine, lisinopril, labetalol and hydrochlorothiazide). Due to recurrent hypokalemia on the neurology department, the internal medicine was consulted. Urinary analysis showed an elevated trans-tubular potassium gradient of 20.1%, suggestive of hyperaldosteronism. Despite current treatment with a beta-adrenergic blocking agent, which lowers renin levels, an ACE-inhibitor, which elevates renin levels and suppresses aldosterone levels, and a thiazide diuretic, which elevates renin levels, a renin-aldosterone ratio was determined. The renin level of 9.7 mIU/l (4.4-46.1 mIU/l) and aldosterone level of 1390 pmol/l (32-980 pmol/l) were suggestive for primary hyperaldosteronism. This diagnosis was confirmed with a saline infusion test (T = 0: renin 0.5 mIU/l; aldosterone 2770 pmol/l; T = 240: renin 0.6 mIU/l; aldosterone 2680 pmol/l), showing renin-independent hyperaldosteronism (Conn’s syndrome). A CT scan showed an unilateral 2 cm adrenal node in the left adrenal gland, suggestive of an adenoma. Adrenal vein sampling was not performed. The patient was treated with an aldosterone-receptor antagonist after which the blood pressure and electrolytes were under control An adrenalectomy is not (yet) performed.

Conclusion: Screening for hyperaldosteronism is warranted in patients with hypertension and spontaneous or diuretic induced hypokalaemia. In our opinion, the use of antihypertensive drugs should not prevent or delay screening for hyperaldosteronism.
Granulomatous mastitis; inflammation with a pituitary origin?

J.J. Engel, C.M.C. Klomp
Elisabeth-Tweestedenziekenhuis, Afdeling Interne Geneeskunde, Tilburg

Case: A 38-year-old woman with a history of prolactinoma, which had proven resistant to dopamine receptor-agonist treatment, but for which she had elected not to undergo adenectomy, was referred to the surgeon in February of 2018 due to swelling of her right breast. An ultrasound showed two echogenic lesions, with prominent ductectasia and bilateral axillary lymphadenopathy. In the following months, recurrent “abscesses” developed with cutaneous fistulas, resistant to surgical and antibiotic interventions. Multiple fluid cultures were positive for *Corynebacterium Tuberculostearicum*. An MRI showed multiple fluid-containing lesions in the right breast. At this point, a possible diagnosis of granulomatous mastitis was put forward. Biopsy showed an inflammatory infiltrate, partly granulomatous, especially around ducti and acini. Patient was started on corticosteroids. During follow-up, the patient reported significantly less pain and signs of inflammation. Pituitary adenectomy was planned.

Discussion: Granulomatous mastitis is a rare inflammatory disease of the breast, of which clinical symptoms can easily be confused with other breast diseases e.g. breast cancer. Its etiology remains unclear, but correlation to breast feeding, ductal injury, hyperprolactinemia, bacterial infection and autoimmune diseases, has been suggested. Multiple of these risk factors can be recognized in this case, which further alludes to possible interactions between them.

Conclusion: The associations found in this case can grant us further insight into causative factors in inflammatory breast lesions, make us more alert to surgery-resistant breast lesions, and provide us with extra reasons for surgical intervention in prolactinomas resistant to medical therapy.
Treatment of Severe Hypotonic Hyponatremia: Efficacy and Safety of 100 or 250 ml NaCl 3.0%

M.E. Roerink, D. Haverkort, M. van Borren, H. de Boer
Rijnstate, Afdeling Interne Geneeskunde, Arnhem

Background: Severe Hypotonic Hyponatremia (SHH, defined as a plasma Sodium ≤ 120 mmol/L) may induce fluid shifts causing cerebral edema and neurological symptoms. This usually requires immediate correction with NaCl 3.0%, to induce a rapid initial rise in plasma sodium of 5 mmol/L to reduce cerebral cell swelling. However, overcorrection may lead to central demyelination. The optimal infusion volume is still under debate.

Methods: All patients admitted between March 2017 and March 2018 with a plasma sodium ≤ 120 mmol/L were included. Patient information was collected retrospectively, including diagnosis at admission, initial treatment, sodium concentrations during treatment, etc.

Results: 95 patients were included. Mean sodium at admission was 1164 mmol/L. SIADH (n = 32) and sodium depletion (n = 32) were the most common diagnoses. NaCl 3.0% bolus treatment was given to 69 patients: 100 ml in 31 patients, 250 ml in 28, and a variety of other doses in 10. Twenty-six patients received other treatments (NaCl 0.9%, fluid restriction, or no treatment). Mean plasma sodium increased by 3.9 ± 2.2 mmol/L in the ‘250’ group, and by 2.4 ± 2.1 mmol/L in the ‘100’ group (p = 0.017). Overcorrection of plasma sodium, defined as a rise > 10 mmol/L within the first 24 hours was not observed.

Conclusions: Severe hyponatremia can be safely treated with 250 ml NaCl 3.0%, and this is more effective than treatment with 100 ml. Cases of overcorrection were not observed.
Case: A 19 year old women was presented to the outpatient clinic with severe polyuria and polydipsia which woke her up every half hour at night. Her blood pressure was 130/85 mmHg. Laboratory investigation showed a sodium level of 139 mmol/L and an osmolality of 286 mOsm/kg. A 24 hour urine collection showed a volume of 19 liters. The urine sodium was < 190 mmol/24 uur and the osmolality in a urine portion was 61 mOsm/kg. She was treated with a vasopressin analogue to reduce her urine production which enabled her to sleep through the night. To differentiate between primary polydipsia and diabetes insipidus a water deprivation test was performed. After 2.5 hours of water deprivation the patient developed severe complaints of dizziness and nausea and the osmolality had risen from 297 to 320 mOsm/L. The urine production remained 1210 ml/hour and the osmolality was 79 mOsml/kg. The rest of the test results after admission of a vasopressin analogue showed evidence for a central cause of diabetes insipidus. No other pituitary hormones were affected. An MRI was conducted which showed enlargement of the pituitary gland with suspicion of a mass of 13 mm and thickening of the pituitary steel. Differential diagnosis consists of an pituitary adenoma, Langerhans histiocytosis, sarcoidosis or hypophysitis. The diagnosis will be presented at NIV dagen 2019...
Re-evaluation of Plummer’s High Dose Iodine Therapy as Last Resort Treatment for Graves Hyperthyroidism

H. Bahrar, G.S. Bleumink, A.C. Bon, M.M.G.J. van Borren, C.F.J.M. van Blanken, J.M.M. de Boer
Rijnstate, Department of Internal Medicine, Arnhem

Background: In 1924, Plummer reported about the efficacy of high dose iodine therapy to establish euthyroidism prior to thyroidectomy for Grave’s disease. After the introduction of anti-thyroid drugs (ATD) this approach gradually disappeared from clinical practice.

Objectives: To re-examine the efficacy of high dose iodine therapy to achieve euthyroidism rapidly, prior to surgery, in patients not tolerating ATD

Methods: Retrospective analysis of patients treated with high dose potassium iodine (KI) for hyperthyroidism due to Graves’ disease.

Results: From July 2013 to May 2018, 20 patients (6 men, 14 women) were admitted for treatment with KI 250 mg tid. Grave’s disease was confirmed by the presence of anti-TSH receptor antibodies in all patients. ATD had to be discontinued because of agranulocytosis (4), allergic skin reactions (6), gastrointestinal side effects (3), hyperthyroidism not responding to high dose ATD (4), and for other reasons (3). KI was administered for 8.9 ± 0.3 days (mean ± SE) and decreased plasma FT4 levels from 45.8 ± 3.2 to 16.6 ± 1.3 pmol/l (mean ± SE, P < 0.001), and FT3 from 18.2 ± 2.9 to 5.7 ± 0.4 pmol/l (P < 0.001). At the day of surgery, FT4 was within the normal range in all but one patient, and FT3 levels were still marginally elevated in 2 patients. Iodine treatment was not associated with side effects.

Conclusion: High-dose potassium iodine treatment remains a safe and effective approach to achieve euthyroidism rapidly, prior to thyroidectomy for Graves’ disease. It is very useful as last resort treatment.
Endoscopic evaluation in patients with newly diagnosed iron deficiency anemia

A. Schop¹, K. Stouten¹, J.A. Riedl¹, R.J. van Houten², J. van Rosmalen¹, F.H.J. Wolfhagen¹, P.J.E. Bindels³, M.D. Levin¹

¹Albert Schweitzer ziekenhuis, Afdeling Interne Geneeskunde, Dordrecht,
²Huisartsgeneeskunde, ³Erasmus MC, Afdeling Statistiek, Rotterdam

Background: Two thirds of patients with newly diagnosed iron deficiency anemia (IDA) are not referred for endoscopic evaluation. Little is not known whether any IDA related diagnosis is made later on in these patients. Two studies describe that 5% of IDA patients are diagnosed with colorectal cancer (CRC) immediately, where 3% of IDA patients display a delayed CRC diagnosis. The effect of a delayed CRC diagnosis on overall survival has not been investigated thus far.

Methods: IDA patients were retrospectively selected from a large cohort of anemia patients, older than 50 years and not known with anemia two years previously, from 2007-2016. Endoscopic and pathological reports, IDA related diagnoses and length of follow-up were collected from the medical files. Early diagnosis was defined as established within 18 weeks after IDA diagnosis. Survival of patients with CRC diagnosis was analyzed using Cox proportional hazards regression.

Results: 587 IDA patients were included with a median follow-up of 4.6 years. In 39% of patients an IDA related diagnosis could be established in-hospital, including 31% early and 8% late diagnoses. In 9% of IDA patients CRC was found, consisting of 11 (20%) late CRC diagnoses. A trend was observed for decreased mortality risk in IDA patients with an early CRC diagnosis adjusted for age, gender and TNM classification (HR 0.32, 95% CI 0.09-1.12).

Conclusion: Almost 40% of IDA patients have an IDA related diagnosis made in-hospital. In a multivariate analysis a delayed CRC diagnosis tented to be associated with poorer overall survival.
Treatment of Severe Protein Malnutrition after Bariatric Surgery

L.N. Deden¹, C. Kuin², F. den Ouden², H. Brandts³, E.J. Hazebroek¹, M. van Borren¹, H. de Boer³

¹Rijnstate, Vitalys, Afdeling Bariatrische Chirurgie, Arnhem, ²WUR, Human nutrition, Wageningen, ³Rijnstate, Clinical nutrition, Arnhem

Background: Severe protein malnutrition, with a serum albumin < 25 g/L, is one of the complications that may develop after bariatric surgery. It is associated with increased morbidity and mortality and requires timely diagnosis and appropriate treatment to prevent rapid clinical deterioration. However, evidence-based recommendations for a specific treatment approach are currently not available. The present study describes the efficacy of a newly developed treatment regimen for post-bariatric patients presenting with severe hypoalbuminemia.

Methods: A single-centre, retrospective analysis of eleven post-bariatric patients presenting with severe hypoalbuminemia, treated with continuous 24h nasal-jejunal tube feeding of a medium chain triglyceride (MCT) formulation in combination with pancreatic enzyme supplementation every 3 hours.

Results: Duration of tube feeding ranged from 25 - 156 days (median 64 days) and pancreatic enzyme was supplemented for 22 - 195 days (median 75 days). An increase in serum albumin levels of 5 g/L and 10 g/L, was achieved after a median period of 20 (range 6 - 26 days) and 36 days (range 21 - 57 days), respectively. Albumin levels were > 35 g/L after a median period of 58 days (range 44 - 171 days).

Conclusion: In this case series, continuous 24h nasal-jejunal MCT tube feeding combined with frequent pancreatic enzyme supplementation was an effective treatment in all patients presenting with severe post-bariatric hypoalbuminemia, without the occurrence of adverse effects.
Severe complication of thiopurine treatment in a young woman with Crohn’s disease

M.P.J. Voet, T.G.A. Calon, R.M. Schreuder
Catharina Ziekenhuis, MDL, Eindhoven

Case: A twenty-eight-year old Caucasian female patient was referred to our emergency department with fever, diarrhea, coughing and visual disturbances. Her medical history reported Crohn’s disease, that was in remission with 6-mercaptopurine during the last four years. Physical examination revealed no abnormalities. Laboratory assessment showed pancytopenia and elevated liver enzymes. Abdominal ultrasound demonstrated splenomegaly, para-aortal lymphadenopathy and a thickened colon wall. Faeces PCR was negative for viruses, bacteria and parasites. CT-scan of the chest showed pneumonitis and extensive lymphangitis suspicious for lymphoma. Subsequently, bone marrow biopsy took place and ruled out a hemophagocytic syndrome or hematological malignancies. Concurrently, serologic tests were performed. Primo Cytomegalovirus (CMV) infection (IgM-positive, IgG-positive) with a viral load of 870,000 IU/ml was detected. The consulted ophthalmologist noticed cotton wool spots. The diagnosis was a systemic CMV infection, affecting gut (colitis), liver (hepatitis), eyes (retinitis) and lungs (pneumonitis). Secondary to the systemic infection, the patient developed splenomegaly, pancytopenia and lymphadenopathy. Anti-viral treatment with intra-venous ganciclovir was initiated. Symptoms, biochemical and radiological abnormalities resolved within 6 weeks.

Discussion: In immunocompetent individuals, CMV infection is usually asymptomatic. The risk of systemic CMV and Epstein-Barr Virus (EBV) infection is increased among individuals who use immunosuppressant’s, like thiopurines. Furthermore, thiopurines are associated with lymphomas. This case illustrates the risks related to thiopurine treatment. Recognition of possible complications is crucial.

Conclusion: Generalized CMV infection is a severe complication of thiopurine treatment. We suggest that routine screening for previous CMV and EBV infections should be considered before thiopurine treatment is initiated.
Supportive treatment of life-threatening upper gastro-intestinal bleeding in a Jehovah's Witness with acute liver failure

K.K.H. Goey, S.A.C. Van Tuyl, S.J.J. Logtenberg
Diakonessenhuis Utrecht, Afdeling Interne Geneeskunde, Utrecht

A 37-year old Jehovah's Witness with a history of fibromyalgia and depression presented with vomiting since three days. She used 3-5 grams of paracetamol and four alcohol units/day since several years. Physical examination revealed tachycardia, fever and abdominal tenderness. Laboratory tests showed conjugated bilirubin 91umol/L, ALP 172U/L, g-GT 1,037U/L, ALAT 6,444U/L, ASAT 26,110U/L, LDH 15,730U/L, and creatinin 553umol/L. We suspected acetaminophen-induced hepatotoxicity and started intravenous rehydration, high-dose proton pump inhibitors (PPI) and N-acetylcysteine. She developed acute liver failure with coagulopathy, hepatic encephalopathy and progressive renal failure. Other causes of acute liver failure were excluded. All Dutch liver transplant centers declined her for potential transplantation due to anemia (hemoglobin 5.4mmol/L) and her refusal of blood transfusion. Therefore, we initiated supportive treatment with ferric carboxymaltose, vitamin K, lactulose, antibiotics and antymycotics. Within days, liver function stabilized.

Days after, she developed melena, suspected for upper gastrointestinal bleeding. The hemoglobin level dropped dramatically to 1.4 mmol/L. Endoscopic intervention was deemed too risky. CT-angiography revealed no active arterial bleeding. Again, supportive treatment was our only option. We minimized blood withdrawals and used capillary blood samples. Coagulopathy was corrected and antifibrinolytics, darbepoetin, PPI and octreotide were administered resulting in cessation of the gastrointestinal blood loss. Hemoglobin level and liver enzymes slowly recovered. After 6 weeks of hospitalization, hemoglobin level reached 4.1 mmol/L, and our patient was discharged.

We describe a case of acute liver failure and severe anemia with limited treatment options. Although blood transfusions seemed crucial, we successfully treated our patient with only supportive measures.
Case: A 53-year old male patient was transferred to our centre because of deterioration of a lower leg ulcer despite topical treatment, split-skin graft, hyperbaric oxygen therapy and high-dose prednisone. Antibiotic therapy was started because of fever, and subsequently a necrectomy failed because of extensive necrosis and an upper leg amputation was performed. Retrospectively, skin biopsy showed circular vascular wall calcium depositions, pathognomonic for calciphylaxis cutis (CC). Renal impairment or hyperparathyroidism were not present, but he was treated with fenprocoumon because of an aortamechanoprothesis, and with hydroxochloroquine, methotrexate, and prednisone (and osteoporosis prophylaxis) for rheumatoid arthritis. He had also type 2 diabetes. Because both the use of warfarin and prednisone have been associated with the development of CC, especially in patients with microvascular disease (e.g. diabetes patients), fenprocoumon was switched to nadroparin, prednisone gradually reduced and osteoporosis prophylaxis stopped. Nevertheless 6 weeks later a new, similar looking ulcer on the right lower leg appeared. Subsequently, nadroparin was switched to enoxoparin for lower calcium load. Natriumthiosulphate, an calcium-chelating agent which has been described to be occasionally effective, was started with healing of the ulcer as result. To date the patient had no recurrence of CC.

Conclusion: Next to classical risk factors like renal impairment and hyperparathyroidism, warfarin, prednisone and chronic inflammatory disorders are associated with development of CC, especially in patients with microvascular disease. Unfortunately, treatment is difficult with limited treatment options. In this case-report we describe a patient with severe CC in whom treatment with natriumthiosulphate was effective.
Unexpected cause of abdominal pain in pregnancy

M.M.C. Hendriks, M.M. Oosterwerff
Catharina Ziekenhuis, Afdeling Interne Geneeskunde, Eindhoven

Case: A 22-year old and six weeks pregnant Tunisian woman was referred to our Emergency Department because of continuous abdominal pain, nausea and vomiting for three days. Her medical history reported umbilical hernia repair during childhood. Physical examination showed a painful young lady, without any particularities at abdominal examination. Laboratory assessment, urine microscopy and vaginal and abdominal ultrasound did not reveal any abnormalities. She was suspected to have constipation and was treated with laxatives. Despite treatment she deteriorated. She developed severe hyponatremia, hyperesthesia of her upper limbs and progressive abdominal pain and was treated with opioids. Regular causes of abdominal pain were excluded. Porphyrin analysis was performed and confirmed the clinical suspicion of acute intermittent porphyria (AIP). She was treated with a high carbohydrate diet and hemin injections for four days whereafter she fully recovered. Mutational analysis for AIP showed a PBGD/HMBS mutation.

Discussion: AIP is a rare autosomal dominant metabolic disorder due to deficient porphobilinogen deaminase activity. Hyponatremia is found in approximately 20% of symptomatic AIP and is often due to inappropriate ADH secretion (SIADH). Attacks are precipitated by factors that induce heme synthesis. Pregnancy appears to exacerbate AIP in some patients. It is unclear whether physiologic changes of pregnancy, medications such as antiemetics or starvation due to hyperemesis are responsible for the first presentation of AIP in this patient.

Conclusion: AIP is a rare and potentially life threatening cause of abdominal pain. Unexplained abdominal pain, hyperesthesia and SIADH could be important diagnostic clues to this uncommon diagnosis.
General practitioner use of internal medicine e-consultations

M. M. E. Krekels¹, D. M. J. Muris², M. Blom³, H. W. M. P. Bergmans³, J. W. L. Cals³

¹Zuyderland M.C., Department of Internal Medicine, Sittard-Geleen, ²Medical Coordination Centre (MCC) Omnes, Medical Coordination Centre (MCC) Omnes, Sittard, ³Maastricht University, Department of Family Medicine, Maastricht

Background: Strengthening primary care – by offering electronic consultation (e-consultation) between general practitioners (GPs) and medical specialists – may be one way to prevent referrals to medical specialist care. An e-consultation is an electronic communication tool allowing GPs to obtain a medical specialist consultant’s expert opinion if there is doubt about a patient-related clinical query. In this observational study we evaluated GP use of internal medicine e-consultations.

Methods: Eligible patients were those in which the GP used an internal medicine e-consultation in 2017 in Zuyderland Medical Centre. Data on demographics, content of the GP clinical query and internal medicine specialist response were retrieved from the GP referral records and hospital medical records.

Results: 82.3% of all 131 GPs in the region used an e-consultation at least once. A total of 428 patients were included, with clinical questions in the e-consultations covering a case-mix of all areas of internal medicine (endocrinology 27.1%, nephrology 24.3%, hematology 22.7%, gastroenterology 14.7% and general internal medicine 11.2%). 20.8% patients (89/428) were referred for a face-to-face outpatient clinic visit within three months follow-up after e-consultation, with no significant difference in age or sex between those referred or not referred.

Conclusion: GPs used e-consultations for internal medicine for a wide range of questions about all areas of internal medicine. The vast majority of the patients could be further treated and managed in general practice after e-consultation. Whether e-consultations reduce the actual number of live outpatient clinic referrals, will be evaluated in a prospective study.
Increased erythrocyte sedimentation rate ‘e causa ignota’ for years; an unexpected twist to the story

L.P.B. Elbers, P.A. Dijkmans, R.J.L.F. Loffeld
Zaans Medisch Centrum, Afdeling Internal Medicine, Zaandam

Case: A 68-year-old woman was referred to the outpatient clinic because of hypokalemia which appeared to be caused by excessive liquorice intake. Her medical history revealed an increased erythrocyte sedimentation rate (50 to 72 mm/h) for over 20 years. She underwent many investigations without ever making a diagnosis. She experienced weight loss, an altered stool pattern, frequent headaches and polyuria. On physical examination, cachexia was striking and an extra beat was heard. There were no signs of heart failure. Hemoglobin level was 7.3 mmol/l and erythrocyte sedimentation rate was 102 mm/h. C-reactive protein, thyroid function, urine screen and stool culture were normal and there was no M-protein. Colonoscopy showed diverticulosis of the sigmoid. Because there was suspicion of a chronic inflammatory process PET-CT scanning was done, which showed some post-infectious pulmonary lesions. Two months after the first presentation she was admitted because of acute thoracic pain. There was no fever and to rule out pulmonary embolism, CTA was performed. CTA-scan surprisingly showed a mass in the left atrium suggestive of a myxoma. Cardiac ultrasound showed an atrial myxoma (5.1 x 3.4 cm). The patients underwent surgery with resection of the myxoma. She had an uneventful recovery and three weeks post-op, her erythrocyte sedimentation rate was lower than ever (46 mm/h) and her weight was stable.

Conclusion and discussion: This case suggests that a smoldering cardiac myxoma, besides the pulmonary lesions, could be the cause of an elevated erythrocyte sedimentation rate. Constitutional symptoms were dominating and cardiac complaints were absent for years.
A 65-year old male patient with an extensive cardiac history and Boerhaave syndrome in his medical history presented with dysphagia for solids and weight loss due to minimal intake. Examination showed a cachexia patient and no other relevant findings. Laboratory findings included acute renal failure (creatinine 498 µmol/L), hyponatriemia, hyperkalemia and elevated transaminase values (ASAT 236 U/L, LD 436 U/L). The ECG showed no acute ischemia.

The patient was admitted to the gastro-enterology ward for further examination and fluid- and feeding support. Gastroscopy revealed no explanation for the dysphagia. Against expectation, the renal function only improved slightly with fluid therapy.

During the hospital admission, we observed discoloured urine. The urine screen came back positive for hemoglobin. A kidney ultrasound was made but showed no abnormalities. Laboratory tests were repeated and revealed a markedly elevated creatine kinase (CK) of 11959 U/L. The diagnosis of a medication-induced rhabdomyolysis was made caused by the combination of rosuvastatine and gemfibrozil.

He was treated with intravenous fluid therapy and rosuvastatine and gemfibrozil were discontinued. Renal function improved and the dysphagia resolved. The other laboratory abnormalities also decreased gradually.

In conclusion, the patient presented with dysphagia as a symptom of rhabdomyolysis. There were only minimal complaints of pain or weakness in the more common muscle groups like upper arms, legs, shoulders and back. Our case exhibits a rare presentation of rhabdomyolysis and underlines the importance of early testing for CK in case of nonspecific symptoms that may be caused by rhabdomyolysis.
Markedly elevated vitamin B₁₂; true or false?

F.M. van der Valk¹, C.B. Brouwer¹, S.G. Heil²

¹OLVG, Afdeling Interne geneeskunde, Amsterdam, ²Erasmus MC, Afdeling Clinical Chemistry, Rotterdam

More and more vitamin B₁₂ is assessed in the “routine” laboratory assay. Whilst vitamin B₁₂ deficiency increasingly gained attention, the evaluation of markedly elevated vitamin B₁₂ is less clear. Here, we present a 42-year old woman who visited her family doctor with fatigue. Due to an isolated elevated vitamin B₁₂ (> 1475 pmol/L) she was referred to our outpatient clinic. The patient’s medical history included a premenstrual syndrome and anxiety disorder for which a tricyclic antidepressant was prescribed. Besides discomfort she had no B-symptoms, neurological symptoms, abdominal pain or changes in bowel habits. Also, vital parameters and physical examination were normal. Additional laboratory testing showed, in addition to the consistently high vitamin B₁₂, a progressive normocytic anaemia (Hb 6.2 mmol/L) and iron deficiency ferritin (7 µg/L).

Such an elevated vitamin B₁₂, in absence of exogenous administration, deserves careful consideration since multiple serious illnesses can be associated (e.g. lymphoproliferative or liver diseases). Also, paradoxal functional vitamin B₁₂ deficiency must be excluded.

Complementary studies in our patient showed no signs for lymphoproliferative disorders or liver abnormalities. Yet, we did find a high methylmalonic acid (0.54 µmol/L), high-normal homocysteine (15 µmol/L) and normal folate (11 nmol/L), suggesting a functional vitamin B₁₂ deficiency. To further understand the falsely elevated vitamin B₁₂ levels in our patient, additional precipitation assays are being performed to assess for interacting antibodies (e.g. intrinsic factor or celiac disease). While writing this abstract we are awaiting these results. Meanwhile, suppletion of both vitamin B₁₂ and iron was prescribed.
Co-trimoxazole induced hyperkalemia and potassium monitoring in hospitalized patients

M.M.E.A. Plantaz1, C. Kramers1,2,3
1Canisius Wilhelmina Ziekenhuis, Afdeling Klinische Farmacie, Nijmegen, 2Canisius Wilhelmina Ziekenhuis, Afdeling Interne Geneeskunde, Nijmegen, 3Radboudumc, Afdeling Klinische Farmacie, Nijmegen

Background: Co-trimoxazole is an antibiotic combination used for Pneumocystis jiroveci pneumonia, as well as for various other indications. Co-trimoxazole is known to increase serum potassium by blockage of the epithelial sodium channel in the distal nephron of the kidney, inhibiting sodium reabsorption and subsequently decreasing potassium excretion. The precise effect size of this adverse drug reaction varies in literature. Co-trimoxazole is most often administered orally, but may also be given intravenously to hospitalized patients.

Methods: In a retrospective cohort study, we aimed to identify the average serum potassium rise after administration of intravenous co-trimoxazole in hospitalized patients. We collected and compared data from patients that received intravenous co-trimoxazole (n = 66) and intravenous ceftriaxone (n = 132) in the period of November 2008 – November 2017.

Results: Change in serum potassium was obtainable in 30 (45%) patients using co-trimoxazole and in 41 (31%) patients using ceftriaxone. Administration of intravenous co-trimoxazole was associated with a significant mean increase in serum potassium, as compared to ceftriaxone (+ 0.55 mmol/L, 95% CI 0.29 – 0.80, p < 0.001). After correction for potential confounders, this effect shrunk noticeably, but remained significant (+ 0.28 mmol/L, 95% CI 0.03 – 0.53, p = 0.031).

Conclusion: In conclusion, intravenous co-trimoxazole is associated with a significant increase in serum potassium and therefore, potassium monitoring should be considered.
Validity and Diagnostic Overlap of Functional Somatic Syndrome Diagnoses

M.L. Joustra¹, S.J.L. Bakker², R.O.B. Gans², J.G.M. Rosmalen²
¹Treant Ziekenhuislocatie Scheper, Afdeling Interne geneeskunde, Emmen,
²UMCG, Afdeling Interne geneeskunde, Groningen

Background: We present the first study that investigates the validity and the diagnostic overlap of the three main functional somatic syndrome (FSS) diagnoses, i.e. chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS), irrespective of help-seeking behaviour or diagnostic biases, and irrespective or arbitrary diagnostic cut-offs with regard to chronicity or symptom interference.

Methods: This study was performed in 79,966 participants of the general-population cohort LifeLines. Diagnostic criteria for CFS (Centers for Disease Control and Prevention), FMS (American College of Rheumatology) and IBS (Rome IV) were assessed by questionnaire. Additional items were added to enable studying the effects of arbitrary cut-offs for minimum symptom chronicity (varying from three for FMS to six months for CFS and IBS), and symptom interference (required for CFS but not for FMS and IBS).

Results: The diagnostic criteria were met by 3.1% for CFS, 6.4% for FMS, and 5.5% for IBS participants. The number of participants that met criteria for all three diagnoses was 48 times higher than what would have been expected based on chance. After alignment of the chronicity and symptom interference criteria to circumvent arbitrary choices in diagnostic criteria, the overlap between diagnoses increased to 153 times. Furthermore, there was a similar pattern of symptom occurrence, particularly for those fulfilling diagnostic criteria for CFS and FMS.

Conclusion: The diagnostic overlap of different FSS was much higher than would be expected by chance, and substantially increased when FSS were more chronic and serious in nature.
A 50-year-old male was referred to our academic bone center because of a non-union dens fracture. Past medical history included type 2 diabetes, ulcerative colitis, primary sclerosing cholangitis, and bisphosphonates for 3 years for osteoporosis (low bone mineral density and a traumatic clavicle fracture). Eight months prior, the patient presented with a sudden inability to move his head, fever and increased C-reactive protein. Initially, head and neck CT was judged as crowned dens syndrome. This is characterized by ligament calcifications and the most frequent cause is calcium pyrophosphate dihydrate crystal deposition disease; it often requires only short anti-inflammatory treatment. Prednisone treatment was started. However, in weeks destructive and expansive osteolysis of the dens arose. Trans-oral bone biopsy of the dens showed plasma cells and crystals with negative microbiological tests. Inflammatory markers decreased, but a non-union fracture remained.

Although serum immunoglobulin G4 (IgG4) was within references, pathologic revision demonstrated dense lymphocytic fibrosing infiltrate with > 100 IgG4-positive plasma cells/HPF and an IgG4/IgG ratio of 50%, fitting IgG4-related disease (IgG4-RD). After radiological revision crowned dens syndrome was discarded. Repeat PET-CT without prednisone showed avidity in the medial rectus eye muscle and in the dens.

IgG4-RD has been reported in virtually every organ system and is a rare cause of lytic bone lesions. Histopathology is key to diagnosis. A caveat is that serum IgG4 is normal in half of cases. Critical re-appraisal may alter the working diagnosis at any stage and may draw upon the expertise of a multi-disciplinary review board.
A 26-year-old woman was referred to the outpatient clinic by the ENT physician because granulomatosis with polyangiitis (GPA) was suspected. She had epistaxis and nasal crusting with obstruction for 9 months; she had no other complaints. She stated that she had used cocaine 3-4 years before the start of her complaints. A nasal biopsy showed nonspecific crusted material; the CT showed a large septum defect. Anti-neutrophil cytoplasmic antibodies (ANCA) were positive, with a perinuclear staining pattern. Anti-myeloperoxidase (MPO) was < 1 kU/L, anti-protein 3 (PR3) was 4.6 kU/L.

We evaluated her for systemic involvement of a vasculitis. Physical examination was unremarkable apart from a nasal voice and frequent sniffing of the nose. Urinalysis ruled against glomerulonephritis and routine lab results and a chest X-ray showed no abnormalities. Because of the unusual ANCA staining pattern for GPA (perinuclear instead of cytoplasmic) we considered cocaine-induced midline destructive lesion (CIMDL) as an alternative diagnosis.

To substantiate this suspicion we tested anti-neutrophil cytoplasmic antibodies against human neutrophil elastase (HNE). In literature, amongst patients with CIMDL HNE ANCA are detectable in 84% whereas inpatients with GPA are HNE ANCA almost always negative. In our patient HNE ANCA was weakly positive. At first she denied active use of cocaine, however during follow-up she admitted to active use. This case underlines that the differential diagnosis with a positive ANCA in the setting of nasal midline destructive lesion should include CIMDL, and can be differentiated from GPA by testing HNE ANCA.
Drug-induced liver injury (DILI) associated with whey protein: ‘shake it off!’

A.A.E. Claessens, F.H.M. Vanmolkot
MUMC+, Afdeling Hematologie, Maastricht

Case: A 32-year old man visited our outpatient clinic for a planned evaluation during treatment of a chronic graft versus host disease (GVHD). The chronic GVHD was the result of an allogeneic stem cell transplantation for an acute lymphatic leukemia. The patient also had a chronic hepatitis B infection. Previously, his liver enzymes were mildly elevated, but stable over time. Laboratory testing revealed a strikingly elevated alkaline phosphatase (ALP) of 3385 U/L (< 115 U/L). Other liver biochemistry tests were as follows: gamma-glutamyl transpeptidase 331 U/L (< 55 U/L), aspartate transaminase 54 U/L (< 35 U/L), alanine transaminase 65 U/L (< 45 U/L). The patient was feeling well and reported no use of alcohol, recreational drugs or recent changes in his prescription medications. He had been consuming whey protein shakes during the past three weeks, more than the recommended daily allowance. After discontinuation, liver enzymes returned to pre-existing values within 5 weeks.

Discussion: Our patient developed acute cholestatic liver injury, most likely due to the regular use of whey protein shakes. Only a few cases with DILI caused by dietary supplements have been described so far. Our patient may have been at higher risk for DILI since he was diagnosed with chronic hepatitis B and GVHD. In patients with acute liver injury, clinicians should inquire about use of dietary supplements and consider discontinuation to prevent further damage.
A red and swollen face after raising the arms

V.A. de Weger, F. Stam
Noordwest ziekenhuisgroep, Afdeling Interne Geneeskunde, Alkmaar

A 82-year female patient was seen, because of a swollen right arm, since two weeks. She also reported hoarseness for two days. Her prior history reported multinodular goitre, chronic obstructive pulmonary disease and pulmonary embolism. Her physical examination was unremarkable except for pitting oedema and erythema of her right arm, without a palpable string. When raising both arms (Pemberton’s manoeuvre) the patient developed a red and swollen face within 30 seconds (Pemberton’s sign). Her laboratory tests showed a normal thyroid stimulating hormone level of 0.52 mU/L (normal range 0.3-5.6) and the inflammatory parameters were not elevated. A duplex-ultrasonography of the right arm was without abnormalities. A MRI-scan of the thorax was performed, which showed a large intrathoracic goitre. The goitre compressed the bifurcation of the jugular vein and subclavian vein at the right side, resulting in an obstruction of venous flow. Given the age of the patient she was treated with radioiodine therapy. Six months later the mechanical complaints of her arm and Pemberton’s sign were still present. She refused further treatment with radioiodine as well as surgery. Compression therapy of the arm was prescribed. Pemberton’s sign is now a days rarely seen, because of improvements in the treatment of goitre. Pemberton’s manoeuvre remains however a relevant diagnostic test, to distinguish between swelling as a result of goitre or for example vena cava superior syndrome and a thromboembolic event.
An uncommon cause of pleuritic chest pain

A.J. Breugom, B.P.C. Hoppe, H. Dik, S. Anten
Alrijne ziekenhuis, Afdeling Longgeneeskunde en Interne Geneeskunde, Leiderdorp

Case: A 56-year old women presented to the emergency department with pain in the left side of the chest and an elevated D-dimer level. Her medical history included resection in the 70s and 80s of an unknown tumour of the stomach, and lobectomy of the right upper lobe from the lung for an unknown tumour. CT scan of the chest demonstrated a large intrapulmonary lesion left dorsobasal with peripheral calcification, and a local pleuropneumonitis.
There was not enough pleural fluid for a diagnostic puncture. A PET-CT scan was performed and showed a lesion of six cm in the left lower lobe of the lung with peripheral calcification, not metabolically active, and a second smaller calcified lesion in the right lower lobe, also not metabolically active. Old medical files were retrieved and showed that the patient had a lobectomy for a pulmonary hamartoma. No biopsy of the pulmonary lesions were performed as the most likely diagnosis is hamartoma. Pleuritic chest pain disappeared spontaneously, and might have been the result of rupture with local pleurisy. Hamartomas are benign mesenchymal tumours which have been reported in lung, liver, or spleen. Pulmonary hamartomas occur mostly as peripheral solitary nodules, but endobronchial hamartomas may also occur. About 30% of hamartomas show characteristic calcification on imaging. Hamartomas are composed of a mixture of mesenchymal and epithelial tissues. Nowadays, PET-CT scan reduces invasive procedures and unnecessary surgical resection.
Neutropenia due to colchicine

S.C.M. Stoof, M. Wabbijn, F.E. de Jongh
Ikazia ziekenhuis, Afdeling Interne Geneeskunde, Rotterdam

Case: A 59-year old man was admitted at the Cardiology department with dyspnea and weight gain. His medical history included diabetes mellitus type 2, CABG, ICD implantation and atrial flutter for which amiodarone was prescribed but which he never used. Furthermore, he had gout for which he currently only used colchicine (0.5mg twice daily). Physical examination revealed increased CVP, reduced respiratory sounds and pitting edema around the lower extremities. ECG showed atrial flutter. The chest X-ray showed cardiomegaly and pleural effusions. Laboratory results demonstrated NT-pro-BNP > 2000, abnormal liver chemistry and renal failure (eGFR 30 ml/min). He was diagnosed with heart failure, probably triggered by untreated atrial flutter and was treated with intravenous diuretics, inotropics and amiodarone. Liver and kidney functions improved but after 5 days he developed pancytopenia with a leukocyte count of 0.52x10⁹/L. He also complained about stomach and muscle aches and diarrhea.

Diagnosis: Colchicine intoxication probably due to acute kidney injury and possibly aggravated by amiodarone (a moderate CYP3A4 and Pgp-inhibitor that could have increased colchicine levels).

Management: Colchicine was stopped and due to the patient’s general poor condition he was treated with G-CSF for 2 days with resolution of neutropenia. Also the stomach and muscle aches and diarrhea resolved.

Clinical relevance: Colchicine intoxication usually starts with gastro-intestinal symptoms which should warrant termination or dose-reduction. Colchicine can induce severe bone marrow suppression; G-CSF can be used to shorten the duration of severe neutropenia. According to Dutch guidelines colchicine should not be used as a long-term (solo) treatment.
A 46-year-old man presented to the surgeons with an acute abdomen. He was diagnosed with an internal hernia due to previous gastric bypass surgery. Over the next 10 days he had serial small bowel resections and a washout because of an anastomotic leak. Metoclopramide was prescribed as an anti-emetic. During the course of his admission the patient became delirious and was started on Haloperidol. One night the patient was increasingly confused and developed torticollis and rigidity of the extremities. The on call psychiatrist suspected an extrapyramidal disorder. The patient was given a total of 9mg Biperiden. The following morning there was no significant improvement in the patient’s confusion, though the rigidity had subsided. He was reviewed by the Internal Medicine and Neurology liaison teams. Tachycardia, fever, but no signs of meningism or hyperreflexia were noted. A hyperthermic toxidrome was suspected. Neuroleptic malignant syndrome was considered unlikely because of a normal CK. Strikingly, despite his fever the patient did not sweat, making an anti-cholinergic syndrome likely. A trial of Physostigmine was administered, resulting in an immediate improvement of the patient’s confusion, motor symptoms and a return of sweating. Toxidromes should be considered in hospital inpatients with unexplained symptoms using multiple prescription drugs. All physicians should be familiar with the symptoms and signs of the most common toxidromes and their treatment.
Reduced grip strength and gait speed in elderly are related to adverse outcomes

J.J. Zwartjens, M. Zeeman
Deventer Ziekenhuis, Afdeling Interne Geneeskunde, Deventer

Background: Frailty is a term used to describe the overall condition of the elderly. The determination of degree of frailty can be time-consuming and is generally difficult. The physical frailty phenotype (PFP) is the most commonly used instrument for assessing frailty. It consists of 5 components: unintentional weight loss, reduced grip strength, poor endurance, reduced gait speed and low physical activity level. It is not known whether reduced grip strength and gait speed alone are related to adverse outcomes (hospitalization, falls, death) and sufficient for assessing frailty.

Methods: This is a retrospective cohort study in patients of the geriatric outpatient clinic of Deventer Hospital. Grip strength and gait speed were measured as standard procedure. Cut-off values were grip strength ≤ 18 kg for women, ≤ 30 kg for men and gait speed ≤ 0.76 m/s, respectively. Follow-up lasted until 6 months after measurement, to record whether adverse outcomes had occurred.

Results: Grip strength and/or gait speed was measured in 492 patients. After correction for confounders, only reduced grip strength and the combination of reduced grip strength and gait speed was associated with adverse outcomes (OR 3.807 (95% BI: 1.757-8.248) and 2.073 (95% BI: 1.092-3.933)).

Conclusion: Reduced grip strength and the combination of reduced grip strength and gait speed are independently associated with adverse outcomes. The combination seems best to assess the risk of adverse outcomes.
Efficacy and safety of octreotide as treatment for severe gastrointestinal bleeding in hereditary hemorrhagic telangiectasia patients: results of a prospective phase II clinical trial

K.V. Grooteman¹, S. Kroon², R. Snijder², J.J. Mager³, J. Tenthof-van Noorden², E.J.M. van Geenen³, J.P.H. Drenth¹

¹OLVG, Afdeling Interne Geneeskunde, Amsterdam, ²St. Antonius Ziekenhuis, Afdeling Longziekten, Nieuwegein, ³Radboudumc, Afdeling Maag-, Darm- en Leverziekten, Nijmegen

Background: Gastrointestinal telangiectases in hereditary hemorrhagic telangiectasia (HHT) patients can cause recurrent bleeding with refractory anemia. Current treatment for gastrointestinal bleeding in HHT is mostly symptomatic due to lack of effective treatment options. Octreotide has shown to inhibit angiogenesis and modifies splanchnic blood flow which may decrease gastrointestinal bleeding. This study was designed to assess safety and efficacy of octreotide in HHT patients with refractory gastrointestinal bleeding.

Methods: In this prospective phase II clinical trial patients received 20 mg octreotide LAR monthly for six months. The primary outcome was the decrease in number of blood transfusions and iron infusions required during the study period compared to six months prior to inclusion. Secondary outcomes included adverse events, quality of life, fatigue symptoms, epistaxis severity score, hemoglobin and ferritin levels.

Results: Ten patients of which 5 (50.0%) female, with a median age of 59.9 years (interquartile range (IQR) 52.3 – 64.8) were enrolled. The median number of blood transfusions decreased from 15 before inclusion to 10 (p = 0.075) during treatment for blood transfusions and 4.0 (IQR: 1.8 – 10.8) to 3.0 (IQR 2.0 – 9.3) for iron infusions (p = 0.74). Patients reported less physical fatigue (16.0 vs. 13.0, p = 0.02) on the MFI-20 scale. The quality of life and the epistaxis severity score showed a tendency of improvement. No serious side-effects were observed.

Conclusion: Octreotide might be a good alternative therapy for HHT patients with gastrointestinal bleeding. Further research in a larger study population preferably with a control group is needed.
Extensive bleeding after bone marrow biopsy: temporary acquired von Willebrand syndrome

T.A. Jansen, A.H.E. Herbers
Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, ’s-Hertogenbosch

Case: a 78-year-old female presented with temporary bleeding and progressive pain of her right leg after bone marrow biopsy, performed because of progressive thrombo- and leukocytosis. Her medical history included Crohn’s disease, for which she was treated with infliximab and a JAK2V617F+ essential thrombocytosis (ET). Laboratory results showed anemia (Hb 5.7mmol/L), thrombo- and leukocytosis (1801x10⁹/L and 134.2x10⁹/L, resp.), haptoglobin 0.88 g/L, total bilirubin 5mmol/L and LDH 1476U/L. aPTT and fibrinogen where normal whereas PT was slightly prolonged (16 sec). CT-angiography excluded an active blush and showed a large hematoma in the gluteus medius muscle.

The combination of ET and extensive bleeding after bone marrow biopsy made us consider acquired von Willebrand syndrome (aVWS). A decreased Von Willebrand factor ristocetin cofactor activity (VWF:RCo)/von Willebrand antigen (VWF:Ag) ratio of 0.50 and reduced level of VWF multimers confirmed our suspicions.

Patient was admitted and treated with multiple gifts of desmopressin and high doses of hydroxy-carbamide. Hereafter, thrombocyte levels decreased to 569x10⁹/L and the VWF:RCo/VWF:Ag ratio normalized (0.74), indicating that the aVWS was cured.

Discussion: acquired type 2A von Willebrand syndrome is a rare disorder. However aVWS is known to be more common in myeloproliferative neoplasms such as ET and might even develop in patients with plateate counts < 1000x10⁹. JAK2V617F is a main driver for the development of aVWS in ET patients. Therefore, this risk should be taken into account by physicians. Moreover if in a patient with ET signs of a bleeding disorder occur tests for the presence of aVWS should be performed.
Pancytopenia, panhypopituitarian and hypoxemia caused by intravascular large B-cell lymphoma

W.R. Kortbeek, F. Jongbloed, J. Wiebolt, E.J. Libourel
St. Franciscus Gasthuis & Vlietland, Afdeling Interne Geneeskunde, Rotterdam

Introduction: Intravascular non-Hodgkin lymphoma is a rare subtype of extranodal large B-cell lymphoma. It may appear in capillaries in different organs and may result in an extremely aggressive clinical course as presented below.

Case: A previously healthy 73-year-old male presented with progressive fatigue and dyspnea d'effort. Physical examination indicated hypoxia, anemia and hepatomegaly. Laboratory tests showed a pancytopenia (hemoglobin 7.4 mmol/L; thrombocytes 125x10^9/L; leukocytes 3.1x10^9/L), hypopituitarism (TSH 0.13mU/L; fT4 8.2pmol/L; testosterone 1.2 nmol/L, relatively low levels of LH, FSH and IGF-1), and elevated CRP, ASAT and LDH. The pituitary-adrenal axis was tested by using the insulin tolerance test and showed an insufficient rise of cortisol. No structural pituitary abnormalities were detected by MRI. CT-scan excluded pulmonary embolism or intra-abdominal pathology except hepatomegaly. Pulmonary ground-glass opacities, traction bronchiectasis combined with a normal BAL raised suspicion of extrinsic eosinophilic alveolitis. Bone marrow aspiration suggested a myelodysplastic syndrome underlying the pancytopenia. Supportive treatment with hormonal suppletion, blood transfusions and oxygen therapy was initiated. Subsequently he developed progressive pancytopenia, dyspnea and liver failure. The combination of symptoms together with the progressive disease course were linked to an intravascular lymphoma. He was admitted to a tertiary center for further treatment and unfortunately died within days because of advanced disease. Additional analysis of the bone marrow indicated intravascular non-Hodgkin lymphoma.

Discussion: Our patient presented three major problems in different organs. The diagnostic process was characterized by finding the overarching diagnosis.

Conclusion: In intravascular large cell lymphoma are symptoms related to organ dysfunction caused by occlusion of blood vessels.
A 39-year old male with a history of severe alcohol and nicotine abuse, liver fibrosis stage F2 and vertebral compression fractures was hospitalized for pancytopenia (hemoglobin 5.4 mmol/L, platelets 21x10⁹/L, leukocytes 1.5x10⁹/L). He had recently started with fluconazole for candida esophagitis. Viral infections and nutritional deficiencies were excluded. As the pancytopenia improved upon discontinuation of fluconazole and alcohol, these factors were considered the likely cause. However, on the day of discharge, the patient’s brother mentioned that dyskeratosis congenica (DC) occurs in the family. Patients with DC have very short telomeres, causing early onset of conditions associated with ageing including bone marrow failure, lung and liver fibrosis, changes in skin pigmentation, nail dystrophy and osteoporosis. The family tree revealed an autosomal dominant inheritance mode of DC. Genetic testing yielded a known mutation in the TERC gene, associated with DC. Bone marrow examination showed a trilineage dysplasia but no cytogenetic abnormalities, which could be the result of myelotoxicity by alcohol or a myelodysplastic syndrome. As the patient had resumed drinking, this could not be repeated. Further work-up revealed osteoporosis and an early stage of lung fibrosis.

**Discussion:** This patient had signs of telomere disease including bone marrow failure, liver fibrosis, lung fibrosis and osteoporosis. However, these disorders can also be the consequence of alcohol or nicotine abuse, which complicates diagnosis and treatment. The family history appeared decisive in the diagnostic process.

**Conclusion:** In this case, the combination of dyskeratosis congenica and substance abuse caused early onset of conditions associated with ageing.
A 79 year old woman in formerly fit condition was referred to our emergency department with a seven day history of progressive difficulty bearing weight on the left leg. The upper leg was painful with asymmetrical redness and swelling. She had a high serum lactate dehydrogenase level (LD, 910). After excluding deep venous thrombosis using ultrasonography, CT and subsequent MRI revealed a mass in the pancreatic head with intense restriction of diffusion, exhibiting mesenterial depositions and infiltration of several vessels. Additionally, the upper muscle compartments of the left leg showed edematous swelling consistent with inflammatory myopathy. Assuming a diagnosis of unresectable advanced pancreatic cancer with paraneoplastic myositis, we informed the patient of her likely very poor prognosis. However, tissue biopsy of both the pancreatic mass and the upper leg muscles showed diffuse large B-cell lymphoma (DLBCL). Although her symptoms were responsive to prednisolone (1mg/kg), the patient willfully refrained from receiving potentially curative chemotherapy and died.

DLBCL mimicking pancreatic carcinoma is rare: Alomari et al. showed that in 1346 fine needle aspirations of pancreatic masses only two cases of DLBCL were identified [Cytojournal, 2016]. In our case the elevated LD, atypical musculoskeletal involvement and intense restriction of diffusion on MRI are not typical for pancreatic carcinoma. Moreover, mesenterial metastases are rarely seen. Despite the absence of lymphadenopathy and splenomegaly, lymphoma should have been considered early on. Since DLBCL stage IV is a curable disease, this case underscores the pivotal role of histopathology in the diagnosis of malignancy.
A 64-year-old patient was acutely admitted because of poor clinical condition caused by hypercalcaemia due to multiple myeloma IgA lambda stage III with unfavourable cytogenetic prognosis. Therapy with bortezomib, thalidomide and dexamethasone was started. On day 3 of therapy (day 5 of admittance), she developed headache with seizure with sequelae afterwards right hemiparesis and cortical blindness. CT-brain showed a hypodensity located parieto-occipital in white matter with leftsided posterior swelling. Neurologic consultation raised suspicion of infarction, to differentiate from of myeloma localization, MRI-brain was performed. It showed nonspecific hyperintensity in the white matter of the parieto-occipital lobes, suggesting edema. This finding, together with clinical course raised suspicion of a posterior reversible encephalopathy syndrome. Bortezomib and thalidomide were discontinued, nevertheless on day 6 patient neurologic situation deteriated with decreased consciousness. Repeated CT-brain showed increased diffuse edema, admission to IC and treatment with labetolol followed. Thereafter her neurological, clinical and laboratory condition recovered with release from hospital on day 25. Her multiple myeloma treatment was resumed with lenalidomide and prednisone without any complication.

**Conclusion:** Posterior reversible encephalopathy syndrome (PRES) is characterized by headache, altered consciousness, seizures and visual disturbances. Neuro-imaging is obligatory to confirm diagnosis showing bilateral areas of white matter edema in the posterior cerebral hemispheres. Causes of PRES are mostly underlying disease and medication. Besides highlighting a rare disorder, this case underlines the importance of early recognition. Early treatment prevents cerebral damage and improves the reversibility of PRES.
Case: A 37-year old woman, without relevant medical history except for a recent uncomplicated delivery, presented to the emergency department with upper abdominal pain, nausea and lose stools without blood for 2.5 weeks unresponsive to antibiotics for a urinary tract infection. Physical examination did not reveal any abnormalities. C-reactive protein was 17 mg/L with a leukocyte count of 22 x10^9/L, with 49% eosinophils. Ascites without hepatosplenomegaly was seen on abdominal ultrasound. An abdominal CT also showed edematous small intestines. Ascites puncture revealed an eosinophilic exudate. Eosinophilia was also present in a duodenal biopsy. No infectious cause was found for the eosinophilia, especially parasitical tests and tuberculosis tests were negative. Antinuclear antigens and the extractable nuclear antigen SS-A were positive. However, the Schirmer test, fundoscopy, a head and neck examination, HR-CT and pulmonary function tests did not reveal abnormalities. There were insufficient arguments for neither Sjogren’s disease nor eosinophilic granulomatous polyangiitis. Bone marrow examination showed 22% eosinophils, no abnormalities in cytogenetics or flow cytometry. T cell receptor gene rearrangement tests did reveal a small monoclonal T cell population.

Diagnosis: Our patient was diagnosed with an unusual presentation of lymphocytic variant hypereosinophilic syndrome (L-HES). In L-HES a small clonal T cell population is the driver for eosinophilia which may result in an elevated IgE and polyclonal hypergammaglobulinemia with associated symptoms.

Management: Treatment consists of prednisone in the acute setting and PEG-interferon for recurrent disease.

Clinical relevance: In patients with eosinophilia without secondary causes a bone marrow examination should be performed.
Is first-line R-CHOP always a good idea? A >10-year population-based cohort identify ‘real-world’ diffuse large B-cell lymphoma patient subgroups in need of new upfront therapies

H.T. van der Galiën1, N.J.G.M. Veeger1, R. Kibbelaar1, H. Storm1, E.G.M. de Waal1, M. Hoogendoorn1, H. van Kamp4, G.J. Veldhuis5, B.P. van Rees6, T. van Meerten7, R.S. van Rijn1


Background: About 40% of diffuse large B-cell lymphoma (DLBCL) patients fail standard chemoimmunotherapy (R-CHOP) and their prognosis is poor. Recently, several novel targeting drugs have been developed. However, applicability and efficiency of these drugs in practice is unclear, as ‘real-world’ data are scarce. In this study, we aimed to distinguish ‘real-world’ patient subgroups that would benefit most from new treatments.

Methods: All DLBCL patients diagnosed between 2005 and 2018 from our population-based HemoBase registry® in Friesland, The Netherlands were included. Fully detailed patient characteristics and outcomes for all lines of treatment were collected. Kaplan-Meier survival analysis was performed.

Results: 558 patients (median age 70 years, 53.8% male) were included. Median follow up was 6.3 years. PFS and OS at 4 years were 60% and 55%. 69 patients (12%) received no treatment or palliative treatment only (median age 83 years, p < 0.01) and worse WHO performance status (84% ≥ 2, p < 0.01). 314 patients (65%) achieved continuous complete remission. 61 patients (12%) did not complete treatment due to toxicity or death. Salvage therapy was initiated in 35% of refractory (median OS 1.3 years) and 41% of relapsed DLBCL (Median OS 6.0 years). Only 17% of R/R patients underwent ASCT with a continuous curation rate of 63%.

Conclusion: In this population-based DLBCL cohort, primary palliative patients, patients who did not complete first-line treatment and patients with refractory disease comprised a substantial group of 34% of all DLBCL patients with exceptionally poor prognosis. These patient subgroups might benefit from less toxic and improved up-front novel therapies.
Eosinophilia in a patient with MPO-ANCA vasculitis: not always an obvious diagnosis

M.C. Slot, J. Potjewijd, P. van Paassen
Maastricht UMC, Department of Internal Medicine, Maastricht

Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by asthma and eosinophilia accompanied by vasculitis and MPO-ANCA in approximately 50% of patients.

Case: A 52-year old patient with a history of end stage renal disease due to relapsing MPO-ANCA vasculitis was evaluated for a 4-month history of recurrent fever. She was dialysed via a central venous catheter but blood cultures were repeatedly negative. The patient experienced bloody crustae from her nose and coughing with sputum but cultures were negative. Laboratory results showed BSE 45mm/h, eosinophilia (1260*10^6/L) and a positive MPO-ANCA level. Flow volume curves were normal but single-breath diffusion capacity (DLCO) was reduced to 60% with nodules and ground glass on HRCT. Considering a relapse of EGPA, a PET CT was done showing attenuation of large vessels, spleen and lymph nodes. Broncho-alveolar lavage showed extreme eosinophilia, consistent with eosinophilic pneumonitis probably related to EGPA. Before we could start with immunosuppressive treatment, abdominal ultrasound showed a renal cell carcinoma (RCC) on the right side which needed treatment first.

After extirpation of the RCC, the fever disappeared as well as the inflammation and eosinophilia. Follow-up HRCT and DLCO normalized. No immunosuppressive therapy was given. Immune activating phenomena in RCC have been well described; however, eosinophilia associated with RCC is rare. Interleukin-5 production by tumor cells plays an important role. We hypothesize that the previous diagnosis of EGPA contributed to susceptibility for eosinophilic pneumonitis and vasculitis.

Conclusion: Eosinophilia and eosinophilic pneumonitis as paraneoplastic phenomenon with renal cell carcinoma in a patient with EGPA.
An aggressive unknown side effect of PCSK9 inhibition?

M.H. Busch, B.P. Jallah, J. Potjewijd, P. Van Paassen
MUMC+, Afdeling Interne Geneeskunde - klinische immunologie en allergologie, Maastricht

A 56-year old male known with dyslipidemia and peripheral arterial disease presented at a community hospital with ulcerative and necrotic wounds of the pelvic region and upper legs. A CT-scan revealed aortoiliac occlusive disease but sufficient vascularization of the groin region. A skin biopsy, necrotomy and partial penis amputation were conducted and showed staphylococcus aureus infection. Due to deterioration of the wounds under systemic antibiotics, the patient was referred to our department. Clinical and histological findings were consistent with pyoderma gangrenosum (PG). Antibiotics, topical tacrolimus and intravenous immunoglobulins were given as proven effective therapy during potential infection. After an initial improvement, the wounds however deteriorated without evidence of infection. Therefore, oral cyclophosphamide and prednisone were prescribed, resulting in an impressive improvement of skin defects of the pelvic region and upper legs. After several months of revalidation, the patient is doing well with oral tacrolimus as maintenance therapy.

In conclusion, PG is a rare inflammatory dermatosis and associated with immune-mediated diseases such as inflammatory bowel disease and malignancy. An extensive work-up was negative for associated clinical conditions. The patient later reported that the wounds started at the site of the first alirocumab (PCSK9-inhibitor) injection. Hypersensitivity reactions due to PCSK9-inhibitor injections have been described previously, but no cases of PG have been reported. Either needle injection or (systemic) drug interactions might lead to the development of PG. In this case, considering the localization and chronology of events, PCSK9-inhibitor therapy might have triggered PG and has therefore been registered at Lareb.
Secondary hemophagocytic lymphohistiocytosis (HLH), a life-threatening disorder, is characterized by excessive macrophage activation, subsequent autophagy of hematologic cells, and multi-organ failure. Various factors affecting immune homeostasis, i.e. infection, autoinflammation, and hematologic neoplasms, can trigger secondary HLH. A 48-year-old male Caucasian presented with fever spikes, weight loss, oral ulcers, and vasculitis-like skin lesions. History revealed schizophrenia treated with clozapine and HLA-B27-positive uveitis. Blood tests revealed pancytopenia, absent lymphocytes, elevated liver enzymes, and high ferritin (60,000 g/L). Bone marrow aspirate showed invasion of macrophages and hemophagocytosis, indicating secondary HLH. Surprisingly, an unusual severe hypogammaglobulinemia was discovered without evidence of genetic abnormalities associated with immunodeficiency syndromes. However, an extreme vitamin-C deficiency was identified with clinical signs of scurvy, likely aggravating the observed immunodeficiency. Moreover, clozapine appeared to worsen the observed hypogammaglobulinemia, further complicating clarification of its exact etiology. Regarding secondary HLH, active infections were ruled out, PET-CT showed no solid tumors or lymphomas, and intravascular lymphoma was excluded by skin biopsy. Radiologic imaging revealed sacroiliitis, which in combination with the aforementioned findings pointed towards an underlying autoinflammatory condition. In the face of acute deterioration, treatment with intravenous immunoglobulins, methylprednisolone, IL-1β-antagonism and calcineurin inhibition was initiated. Due to refractory disease, treatment was modified to etoposide. Follow-up PET-CT revealed new lymphadenopathy. Excised lymphoid tissue showed vast presence of mycobacterium avium, which shortly thereafter disseminated despite broad antimycobacterial therapy, creating a staggering dilemma in an already unusually challenging HLH presentation: treat the disease risking fatal infection or focus on fighting infections, always a step behind?
Persistent parvovirus B19 viremia associated chronic fatigue syndrome

M. Salih1, J.W.J. van Esser2, P.L.A. van Daele1
1Erasmus MC, Afdeling Inwendige Geneeskunde, Rotterdam, 2Amphia ziekenhuis, Afdeling Inwendige Geneeskunde, Breda

Case: An otherwise healthy 42-year-old female presented with an acute parvovirus B19 viremia, likely transmitted by her son. After an initial acute phase, she developed chronic crippling fatigue. Work-up revealed hemolysis and splenomegaly, without evidence of hematologic malignancy or immunodeficiency. Meanwhile, the parvovirus B19 viremia persisted for months with detectable IgM antibodies with further increase in debilitating fatigue. She was admitted and treated with intravenous immunoglobulin (IVIG) therapy. This drastically improved her symptoms, as self-reported in chronic fatigue syndrome scales. Parvovirus B19 viremia and IgM antibodies persisted despite treatment. Unfortunately, her fatigue returned 3 months later and a second course of IVIG and vitamin C marginally improved her symptoms. General treatment for chronic fatigue syndrome (CFS) has been initiated and its effect remain to be determined.

Discussion: CFS due to persistent human parvovirus B19 viremia has been reported in otherwise healthy subjects without an apparent immunodeficiency. Two caveats need to be considered. First, delayed clearance of the virus for up to two years has been described in asymptomatic patients. IgM antibodies, however, are usually cleared after 2 months and may therefore be a better marker. Second, it is unclear why the virus is not cleared in otherwise healthy individuals and how it contributes to CFS. Treatment with IVIG is based on case series of immune compromised (HIV) patients.

Conclusion: Screening for chronic parvovirus B19 viremia in patients with CFS is not recommended, but could be considered if fatigue was preceded by symptoms suggestive of an acute parvo B19 viremia.
Be aware of nitrofurantoin hypersensitivity reactions

M.F. Schmitz, A.H.E. Herbers
Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, ’s-Hertogenbosch

A 73-year old man, with no relevant medical history, was referred because of eosinophilia (eosinophils absolute count 9.2 x 10^9/L). He presented with dyspnea, blurred vision, warm feeling but no fever, and a rash since two weeks. The symptoms already started to improve at the time of the first consult. One week prior to the consult, the patient had been treated for a urine tract infection with nitrofurantoin during one week by his general practitioner. Physical examination showed no abnormalities. There was no rash or fever at the time of the consult. The laboratory blood tests were repeated. This showed complete normalization of eosinophil count and improvement of other reactive inflammatory parameters. The chest radiography was normal. There was no need for further diagnostic evaluation or treatment, the patients symptoms resolved completely. The symptoms started shortly after taking nitrofurantoin and resolved spontaneously after cessation of this drug. On the Naranjo Scale this reaction scored 7 points, indicating a probable adverse drug reaction. A hypersensitivity reaction to nitrofurantoin is the most likely diagnosis. Literature suggests an immunological mechanism, possibly type 3 hypersensitivity. Pulmonary syndrome caused by nitrofurantoin can be either acute or chronic and is often accompanied by eosinophilia. Initially these reactions are frequently misdiagnosed and then can cause morbidity and mortality. Therefore it is important to know of and recognize these reactions to nitrofurantoin. The solution is simple and effective; to stop nitrofurantoin and avoid future use will prevent reactions and related morbidity.
In chronic Q fever patients MMP1 single nucleotide polymorphism (SNP) rs7125062 is inversely associated with complications and P2RX7 SNP rs3751143 is associated with therapy failure

S.B. Buijs¹, A.F.M. Jansen¹, J.J. Oosterheert¹, T. Schoffelen², P.C. Wever¹, A.I.M. Hoepelman¹, E. van de Vosse⁴, M. van Deuren³, C.P. Bleeker-Rovers²

¹University Medical Center Utrecht, Department of Internal Medicine and Infectious Diseases, Utrecht,
²Radboud university medical center, Department of Internal Medicine and Infectious Diseases, Nijmegen, ³Jeroen Bosch Hospital, Department of Medical Microbiology and Infection Control, 's-Hertogenbosch, ⁴Leiden University Medical Center, Department of Infectious Diseases, Leiden

Background: Chronic Q fever is a persistent infection with the intracellular bacterium Coxiella burnetii. Genes encoding for matrix metalloproteinases (MMPs) which cleave extracellular matrix, pattern recognition receptors that recognize C. burnetii, and phagolysosomal pathway components that kill intracellular micro-organisms are known to play a role in the development of chronic Q fever. We evaluated the association between SNPs located in these genes and clinical outcome of chronic Q fever patients.

Methods: SNPs involved in immune response to C. burnetii were selected from previous SNP association studies and determined in a cohort of proven and probable chronic Q fever patients. The primary outcome was all-cause mortality; secondary outcomes were chronic Q fever-related complications and therapy failure. Subdistribution hazard ratios (SHR) were calculated.

Results: Nineteen SNPs were analyzed in 134 proven and 29 probable chronic Q fever patients. SNP rs7125062, located in MMP1, was inversely associated with chronic Q fever-related complications (SHR 0.49 (95% CI, 0.29-0.83), p=0.008). SNP rs3751143, located in P2RX7, was associated with therapy failure (SHR 2.42 (95% CI, 1.16-5.05), p = 0.02). This is in line with other reports, showing loss-of-function of the P2RX7 receptor leading to inefficient killing of intracellular organisms. None of the selected SNPs was associated with all-cause mortality in multivariable analysis.

Conclusion: A polymorphism in P2RX7, known to lead to loss-of-function of the receptor and inefficient killing of intracellular organisms, and a polymorphism in MMP1, known to lead to lower MMP1 expression in blood, were associated with clinical outcomes in chronic Q fever patients.
Outpatient Parenteral Antimicrobial Therapy (OPAT): clinical experience from a secondary referral teaching-hospital

A.M. den Harder, A. Robben, N.H.M. Renders, M. van Apeldoorn
Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, ‘s-Hertogenbosch

Background: Outpatient Parenteral Antimicrobial Therapy (OPAT) is used for several years in the Netherlands. It reduces the duration of hospital stay and the risk of hospital-related infections while it increases patient satisfaction and quality of life. Data regarding the application of OPAT in the Netherlands are however scarce.

Methods: Patients who received OPAT between June 2018 and August 2018 at the Jeroen Bosch Hospital were included. Information about patient characteristics, OPAT indication, type of antimicrobial and complications was extracted from the electronic patient file.

Results: In total 34 patients with an average age of 64 years were included. OPAT was most frequently applied by the Department of Urology, Neurology, Pulmonary Medicine and Orthopaedics. Indications were bacteraemia (18%), urinary tract infection (18%), infection of joint prosthesis (13%) or other (49%). Average duration of OPAT was 12 days. Two patients (6%) developed phlebitis. Two patients (6%) developed side effects of the antimicrobials, warranting a switch in antimicrobial in one patient. OPAT was successfully completed in 32 patients (94%). In patients receiving OPAT 14 days or longer (n = 18), laboratory monitoring was applied in 6 patients (33%). In one patient the laboratory findings warranted a change in antimicrobial. No data about patient satisfaction and quality of life were available.

Conclusion: This study showed that most patients are able to successfully complete OPAT, and the rate of line complications is relatively low. However, protocol adherence could be improved regarding to laboratory monitoring.
External validation and update of prognostic models to predict poor outcomes in hospitalized adults with RSV: a retrospective Dutch cohort study

L.M. Vos¹, J.J. Oosterheert¹, I.M. Hoepelman¹, L.J. Bont¹, F.E.J. Coenjaerts¹, C.A. Naaktgeboren¹
¹UMC Utrecht, Afdeling Interne Geneeskunde/Infectieziekten, Utrecht,
²WKZ Utrecht, Afdeling Kinderinfectiologie, Utrecht

Background: Respiratory syncytial virus (RSV) causes significant morbidity and mortality due to severe respiratory tract infections (RTI). For adults, two models (Park et al, Infect Dis 2016 and Kim et al, J Infect Dis 2014) were developed to predict which patients with RSV infection have poor prognosis, but these are not used regularly. This study externally validates and updates these two models for hospitalized RSV-infected adults to predict poor outcome at the time of initial presentation.

Methods: We retrospectively identified hospitalized adult patients with an RSV(A/B) positive PCR on respiratory tract samples at the time of RTI diagnosis (2005-2018). The primary outcome was in-hospital death and/or Intensive Care Unit (ICU) admission. Missing values were imputed using multiple imputation. We externally validated the two published models and updated the best discriminating model (highest C-statistic).

Results: We included 241 patients (80% community and 20% hospital acquired RSV-infection). Median age was 60.2 years, 56% were male and 69% immunocompromised. In total, 21% (n = 51) had the primary outcome of ICU-admission (n = 41) and/or in-hospital mortality (n = 26). In our cohort, Parks model had a C-statistic of 0.65 (95%CI,0.56-0.74) and Kims model 0.55 (95%CI,0.46-0.64), both with poor calibration. We updated Parks model, leading to addition of urea and confusion. This extended model had a C-statistic of 0.77 (95%CI,0.70-0.86) and good calibration.

Conclusion: We externally validated, updated and calibrated a model predicting ICU-admission or death among adults with RSV-infection. Our model will be useful for targeting early antiviral treatment in patients at high risk of developing life-threatening RSV-infection.
An 86-year old female with a medical history of hypertension, TIA and CKD, initially presented with tenosynovitis, arthritis and dactylitis. After some nodular skin lesions occurred on both legs, the diagnosis of cPAN (cutaneous polyarteritis nodosa) was made based on clinical features and skin biopsy. A rheumatologist started treatment with 30mg prednisone. However, within three weeks, extensive pustular papules and ulcera occurred all over her body. The cutaneous culture revealed Mycobacterium marinum, which was later also found in tenosynovial fluid. Mycobacterium marinum infections typically present as granulomas on arms in people handling sea water or aquaria. Our patient did neither, but watered her garden from a rain barrel, in which we later detected mycobacteria.

The prednisone was tapered and she started on azithromycin, ethambutol and rifampicin. Weeks later, the patient developed a hypercalcemia of 3.9 mmol/l; her skin lesions were barely improved. We hypothesized that the hypercalcemia – similar to tuberculosis - was due to granulomas, which might be supported by: PTH and PTH-rp were low, 1,25- and 25-OH-vitamin-D were high-normal and a PET-scan was negative besides an impressive dermatitis and myositis. After hyperhydration the hypercalcemia recovered but re-occurred days later; further treatment was withheld and the patient eventually died.

This extraordinary case of disseminated Mycobacterium marinum in a former immunocompetent woman is illustrative in several ways: the first symptom was arthritis, a skin biopsy led to a false diagnosis, an extreme hypercalcemia occurred and the probable origin of the Mycobacterium marinum was a rain barrel.
Determining the causative agent and optimal duration of antibiotic therapy in patients with diabetes and foot osteomyelitis: BonE BiOPsy (BeBoP)-trial

M.C.T.T. Gramberg¹, R.S. Lagrand¹, L.W.E. Sabelis¹, M. Nieuwdorp², E.J.G. Peters¹

¹Amsterdam UMC - locatie VU, Afdeling Interne Geneeskunde, Amsterdam,
²Amsterdam UMC - locatie AMC, Interne Geneeskunde, Amsterdam

Aim: The optimal strategy to determine the causative organism in persons with diabetic foot osteomyelitis (DFO) is currently unknown, as is optimal antibiotic treatment duration. The primary objective of this multicentre randomized controlled trial is to compare treatment outcomes of subjects treated with antibiotics based on culture results of bone biopsy versus treatment based on deep wound tissue sampling. An observational part of the study will focus on optimal duration of antibiotic treatment, different microbiological identification techniques and the role of FDG-PET/CT in follow-up.

Methods: Eighty subjects with DFO will be included in a double-blind RCT. Biopsy from wound tissue and bone will be taken before initiation of antibiotic therapy. Forty subjects will be treated based on bone biopsy culture and forty based on cultures of deep wound specimen. After 3 and 6 weeks, bone biopsy and FDG-PET/CT scan will be repeated in ten subjects in each treatment group for an observational part of the study. We will continue treatment for these subjects if either bone biopsy or scan is positive.

Results: Primary outcome measurement is remission of osteomyelitis at 12 months after diagnosis, i.e. clinical cure of infection without need for additional surgery or antibiotics. Outcome measurements of the observational part of the study are: signs of inflammation on follow-up imaging, in bone biopsy culture and molecular microbiological technique and histology.

Conclusions: We hypothesize that antimicrobial therapy of DFO based on bone biopsy culture results will lead to higher rates of remission than therapy based on deep wound culture.
Two diagnoses?

M.M. Suttorp1, L.B. Vrolijk1, M.G.J. de Boer1, J.E. Stalenhoef1,2

1LUMC, Afdeling Interne Geneeskunde, Leiden, 2OLVG, Department of Internal Medicine, Amsterdam

Case: A 36 year old female was referred for second opinion of neuropsychiatric SLE (NP-SLE). Diagnosis of SLE was established according to the SLICC and ACR criteria based on arthritis, oral ulcers, skin sensitivity to sunlight, positive ANA, anti-dsDNA and low C3. The patient also experienced headaches, cognitive dysfunction, tremors and left facial muscle weakness. While treated with plaquenil and prednisone she became manic-psychotic. The rheumatologist concluded that all symptoms combined with brain MRI (aspecific white matter lesions) could fit the diagnosis NP-SLE. However, several tests were ordered to rule out infections and lymphoma before starting treatment and revealed that the pant was HIV-1 positive. The CD4+ lymphocyte count was 20 cells/µl and liquor showed high HIV and CMV load. She was treated for HIV and CMV encephalitis with combined antiretroviral therapy (cART) and ganciclovir. Immunosuppressive medication for SLE was discontinued. After a month, the psychosis had completely resolved and the antipsychotics were discontinued. Within 9 months of follow up, no signs of SLE reappeared.

Discussion: The diagnosis of both HIV and SLE remains difficult and symptoms overlap with other diagnoses. Arthritis, oral ulcers and neurological symptoms could all have been caused by HIV. ANA is nonspecific and positive in healthy volunteers in 5-32%. dsDNA antibodies are specific for SLE, but are also rarely found in other disorders. Nonspecific autoantibodies have been reported in 45% of HIV-infected patients in cART era, which is associated with a reduced CD4-count.

Conclusion: HIV is a heterogenous disease that should never be overlooked.
More than five years after the Dutch Q fever outbreak: Chronic Q fever has not disappeared

S.B. Buijs1, J.J. Oosterheert1, S.E. van Roeden1, L.M. Kampschreur2, A.I.M. Hoepelman1, P.C. Wever3, C.P. Bleeker-Rovers4

1University Medical Center Utrecht, Department of Internal Medicine and Infectious Diseases, Utrecht,
2Medical Center Leeuwarden, Department of Internal Medicine and Infectious Diseases, Leeuwarden,
3Jeroen Bosch Hospital, Department of Medical Microbiology and Infection Control, ’s-Hertogenbosch,
4Radboud university medical center, Department of Internal Medicine and Infectious Diseases, Nijmegen

Background: After infection with Coxiella burnetii, 1-5% of patients develop chronic Q fever. It is not yet known how long the interval between acute and chronic infection can be. Following the 2007-2010 Dutch Q fever outbreak, data from chronic Q fever patients are systematically collected in the Dutch National Chronic Q Fever Database. We evaluated the interval between acute and chronic infection and the mortality rates over time.

Methods: Patients from 45 participating hospitals meeting the Dutch Q Fever Consensus Group criteria for chronic Q fever were included. Chronic Q fever-related complications and mortality were assessed by two authors based on predefined criteria.

Results: In total, 519 chronic Q fever patients were identified. Of these, 313 (60%) had proven, 81 (16%) probable and 125 (24%) possible chronic Q fever. Since the last update in 2016, 61 new chronic Q fever patients had been diagnosed. New patients were more often diagnosed with proven than probable or possible chronic Q fever. The largest observed interval between acute infection and diagnosis of chronic Q fever was 9.2 years. Chronic Q fever-related complications occurred in 213 (68%) patients. In total, 163 (31%) patients died of whom 86 (17%) definitely or probably related to chronic Q fever.

Conclusion: New chronic Q fever patients were still diagnosed more than five years after the largest Q fever outbreak ever reported. New cases are more often diagnosed with proven chronic Q fever. The largest observed interval between acute infection and diagnosis of chronic Q fever was 9.2 years.
Complicated soft tissue infection after laser prostatectomy

C.E.A. Alderweireld, P.T.E. Postema, R.E. Stuurman-Wieringa, H. Boom
Reinier de Graaf Gasthuis, Afdeling Interne geneeskunde, Delft

Case: A 73-year old male with an unremarkable medical history presented to our emergency department with fever since one week and immobility due to pain in his right leg. Eighteen days earlier he underwent a GreenLight laser prostatectomy for bladder outlet obstruction. There was marked erythema and swelling of the right upper thigh and elevated infection parameters. After five days of antibiotic therapy for S. aureus soft tissue infection, fever persisted. CT-scanning because of rapid progression of swelling and pain showed multiple abscesses with air collections. Positive S. aureus abscess, blood and urine cultures revealed a urinary origin, caused by a prostatic fistula. After multiple surgical interventions and prolonged antibiotic therapy with hemodynamic support in the intensive care unit, the patient is now recovering in a nursing home.

Discussion: Bladder outlet obstruction is common in adult men and has various treatment options. Laser prostatectomy is increasingly replacing transurethral prostatectomy as surgical therapy in recent years. Literature shows that both techniques have similar outcomes with respect to efficacy and complication rate. Laser prostatectomy leads to shorter admissions. However, it has also been reported that the use of laser treatment has higher rates of per-operative prostatic capsular perforation, which is thought to be the cause of the fistula leading to soft tissue infection in this case, resulting in a very protracted admission with serious complications.

Conclusion: Although laser prostatectomy for bladder outlet obstruction is increasingly more performed, clinicians should be aware of rare but serious and potential life-threatening complications, as presented.
Guinea pig; friend or foe?

E.A. Reijm, G. Prins-Van Gilst, F.H.M. Mollema, B.P. Ramakers

1Erasmus MC, Interne geneeskunde, Rotterdam, 2RadboudUMC, Afdeling Intensive Care, Nijmegen

Case: A 38-year old Caucasian female, with relapsing-remitting multiple sclerosis, developed fever, a headache, nausea and vomiting and she complained of coughing and dyspnea. She was admitted to the Emergency Department where laboratory results showed elevated inflammatory parameters and an X-ray revealed a pulmonary infiltrate. She went home with amoxicillin. Her condition deteriorated and she was admitted to the internal medicine ward and treated with amoxicillin/clavulanic acid and ciprofloxacin for community-acquired pneumonia. She recovered quickly and went home with levofloxacin. A thorough anamnesis learned that our patient bought two guinea pigs two weeks before she got symptoms. One of them died shortly thereafter due to symptoms of pneumonia. The other guinea pig had conjunctivitis and our patient had to clean his eyes regularly. After discharge from the hospital, the culture of sputum obtained from our patient tested positive for Chlamydia psittaci. Additional analysis demonstrated the Chlamydia caviae subtype. After 6 weeks, symptoms and the pulmonary infiltrate were resolved.

Discussion: Although the zoonotic potential of C.caviae has been described since 2017, only six cases have been reported so far. Remarkably, these cases have only been described in the Netherlands. Although C.caviae pneumonia is rare, it can be potentially life threatening. Given the popularity of guinea pigs as pet animals we feel that both veterinarians and physicians should be aware of this zoonotic potential of C.caviae.

Conclusion: The Gram-negative intracellular bacteria C.caviae was identified as a possible cause of severe community-acquired pneumonia in our patient. Her guinea pigs were the likely source.
A 59 year old woman complained of thoracic pain for two years. Multiple CT-scans showed interstitial disease of the right lung, which remained stable and for which the patient refused additional analysis. Complaints of malaise, weight loss, fever and pain at variable locations prompted her current visit to our hospital. At physical examination the patient had fever and a painful swelling on the left side of her neck. Laboratory results showed a high ESR, normocytic anemia, thrombocytosis and leukocytosis with neutrophilia. Blood cultures were negative. A PET-CT was performed, showing enhanced uptake in the left common carotid artery region and the right lung. No suspect lymph nodes were found. Multiple target echographies showed an occluded vein in the left submandibular gland and wall thickening of the jugular vein without thrombosis, as well as lymphadenopathy. Echocardiography showed normal heart valves. The patient developed jaw claudication and multiple tender swellings on the skin of her arms. The combination of possible septic emboli and an inflammatory disease localized in the neck region was suggestive for Lemierre syndrome, and the patient was started on amoxicillin/clavulanate acid after which both her symptoms and inflammatory parameters resolved. 

**Conclusion:** The important lesson of this case is that Lemierre syndrome may present as a chronic inflammatory condition, with symptoms like jaw claudication, interstitial lung disease, weight loss and fever.
Intentional overdose of dolutegravir/abacavir/lamivudine (Triumeq) in a 26-year-old man

Maastricht University Medical Center, Department of Internal Medicine, Maastricht

Background: Antiretroviral therapy (ART) is prescribed to patients with an HIV infection. Triumeq is a single-tablet regimen comprising the integrase strand transfer inhibitor (INSTI) dolutegravir and the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir and lamivudine. Although it is prescribed frequently, overdoses with Triumeq have not been reported previously.

Case report: We present a case of overdose with Triumeq in a 26-year-old man. Our patient was admitted following an intentional overdose with 30 tablets of Triumeq. He was diagnosed with an HIV-1 infection about one year earlier. The patient suffered no complaints, physical examination showed normal vital functions and laboratory testing revealed a lactic acidosis and stable serum creatinine.

The most commonly encountered toxicity of NRTIs is mitochondrial impairment, which can lead to lactic acidosis. Mitochondrial toxicity results from NRTI-induced inhibition of a mitochondrial DNA polymerase, resulting in dysfunctional mitochondria. Dysfunctional mitochondria are unable to perform their metabolic functions, such as oxidative phosphorylation. Lactate accumulation results from overproduction of lactate by insufficient oxidative phosphorylation.

The incidence and severity of lactate accumulation range widely between different NRTIs. Routine lactate assessment is not recommended in asymptomatic patients using NRTIs. However, in patients with an NRTI overdose acute mitochondrial toxicity must be considered.

In our patient, the lactic acidosis dissolved completely after discontinuation of medication and administration of metabolic cofactors for mitochondrial metabolism (riboflavin, carnitine and thiamine). As Triumeq will be used on a regular basis as treatment for patients with HIV-1 infection, these intoxications are expected to be encountered more often.
An otherwise healthy 19-year-old man visited the emergency department with complaints of vomiting, diarrhoea, fever and chills for four days. He had abdominal discomfort at palpation and a temperature of 39.0°C. Laboratory analyses revealed elevated liver enzymes (ALAT 376 U/L, ASAT 450 U/L, LDH 1,156 U/L, bilirubin 42 µmol/L), thrombocytopenia (64x10⁹/L), increased CRP (32 mg/L), and extremely elevated ferritin levels (13,988 µg/L). The latter was suggestive for hemophagocytic lymphohistiocytosis (HLH). Additional laboratory and physical analyses (fibrinogen 1.8 g/L, triglycerides 2.04 mmol/L, soluble CD25 5,100 U/L, splenomegaly) supported this diagnosis. We suspected a viral cause for HLH. Faecal cultures and serology for EBV, CMV, hepatitis A/B/C/E, HSV, HIV, Parvo-B19, and leptospirosis proved negative. While awaiting hantavirus serology, the patient’s condition improved with supportive treatment, leading to discharge after six days. One week later, follow-up blood samples were tested positive (IgM 1:32, IgG 1:128) to orthohantavirus Seoul-virus (SEOV).

Discussion: HLH is a rare and potentially fatal clinical syndrome, caused by a strong, but ineffective activation of the immune system, and often triggered by infections. We strongly suspected a viral causative agent, which was confirmed by the positive SEOV test. SEOV is part of a family of rodentborne viruses. Human infections with SEOV are rare. Retrospectively, the patient’s girlfriend offered him two domestic rats, which had bitten him repeatedly. The rats were euthanized and tested positive for SEOV.

Conclusion: This is the first human case with a Seoul-virus infection causing HLH. In case of extremely elevated ferritin levels, HLH has to be considered together with a work-up for causative agents, including SEOV.
A woman with Parrots Disease

H.M. Schenk, P.H.P. Groeneveld
Isala, Afdeling Interne Geneeskunde, Zwolle

Case: A 56-year old woman, with a medical history of hypertension, was admitted to the hospital because of a 4-day fever, chills, headache, nausea and anorexia. The previous day, she had returned home from a family vacation in Greece, where her symptoms started. None of the family members had symptoms. On examination, blood pressure was 144/85 mmHg, pulse 85/min, respiratory rate 17/min, oxygen saturation 98% on ambient air, temperature 39.4°C. Auscultation of the lungs revealed crackles in the right lobe. A chest X-ray revealed a pneumonia in the right middle lobe. Laboratory testing showed a normal kidney function and blood count, an increased CRP, mildly increased transaminases, glutamyltransferase and alkaline phosphatase. PCR-analysis of sputum was positive for Chlamydia psittaci, which was later typed as genotype A. Genotype A is associated with Psittaciformes (parrots). She was successfully treated with Moxifloxacin. When PCR results were discussed with the patient, she recalled taking care of a dying bird before her vacation, which was brought home by her cat.

Conclusion: C. psittaci infections in humans are underestimated and annual reports of cases might not reflect the real numbers. C. psittaci can be transmitted to humans by inhalation of contaminated aerosols of excretions from infected birds. Transmission from person-to-person is assumed to be rare. The anamnesis is very important for the correct diagnosis, even when modern technology and diagnostic tools are available.
Acute cholecystitis went viral

V.P. Kuiper, A.E. Scholtens, P.J. de Vries
Tergooi Hospital, Afdeling Internal Medicine, Hilversum

Case: A 29 year old male patient was admitted to our hospital with jaundice, sore throat, cervical adenopathy, headache and fever. His vital signs on presentation were unremarkable and there was slight tenderness in the right abdominal quadrant on palpation. Laboratory findings were notable for lymphocytosis with atypical lymphocytes, thrombocytopenia and cholestatic jaundice (total bilirubin 139 µmol/l, conjugated 132 µmol/l) with mild hepatitis (AST 467 IU/L; ALT 540 IU/L). Transabdominal ultrasonography showed hepatosplenomegaly and thickening of the non-distended gallbladder wall (4 mm) with marked perifocal edema. Sludge was seen in the gallbladder but no gallstones and there was no sign of bile duct distension. Serologic findings were positive for EBV VCA IgM and negative for EBV VCA IgG, but positive for IgG anti EBNA. The EBV viral load was 400 IU/ml (qPCR). The diagnosis acute, acalculous, cholecystitis associated with primary EBV infection was made. A careful expectative approach followed without the initiation of antibiotics. Symptoms and laboratory results gradually improved and he was discharged after three days of hospitalization.

Discussion: Acute cholecystitis associated with primary EBV infection is rare and has been described as acute acalculous cholecystitis. A conservative approach is warranted. Clinicians should be aware of this rare condition which should not be mistaken with the common acute cholecystitis with cholecystolithiasis or sludge in the gallbladder, which is treated by cholecystectomy or gallbladder drainage and antibiotics.

Conclusion: Acute cholecystitis can be a consequence of primary EBV infection and warrants an expectative approach.
Cat Scratch Disease causing Cerebral Venous Sinus Thrombosis?

B.A. Snijer, M. van Apeldoorn, D.J. Nieuwkamp, H.J. Jansen
Jeroen Bosch Ziekenhuis, Afdeling Interne Geneeskunde, 's-Hertogenbosch

Case: A 42-year old male without relevant medical history was referred to our hospital because of blurred vision and diplopia. Three months before he was scratched by one of his kittens, causing a cutaneous papular lesion on his right thumb. Weeks later he developed progressive headache, a self-limiting episode of fever with chills and a painless swelling below the right axilla. He did not get medical help until he developed vision problems.

Neurologic examination showed bilateral papilledema without further neurological deficits. Brain MRI was normal but MRV showed extensive cerebral venous sinus thrombosis (CVST). On additional CT of the neck, thorax and abdomen right axillar lymphadenopathy and splenomegaly with multiple hypodensities were found. Bartonella henselae (BH) PCR on the punctate of the right axillar lymphocele was positive. PCR for BH on cerebrospinal fluid was negative. No other cause for CVST was found. Anticoagulant treatment for CVST was initiated and patient was treated with doxycycline and rifampicin for 14 days because of the suspected relation between CVST and BH infection.

Discussion: This case report suggests a relationship between cat scratch disease (CSD) and CVST. The negative PCR for BH on cerebral fluid does not exclude central nervous system infection, since the sensitivity of PCR testing for BH is low. Literature search yielded only few studies describing a possible association between CVST and CSD.

Conclusion: Cerebral venous sinus thrombosis possibly due to cat scratch disease.
A patient with AIDS and ...

W. van Kampen¹, M.J.T. Blaauw¹, M.A.A. Claassen², R. van Crevel¹

¹Radboudumc, Afdeling Interne Geneeskunde, Nijmegen, ²Rijnstate, Afdeling Interne Geneeskunde, Arnhem

Case: Six months after a 24-year old HIV-infected woman stopped taking her anti-retroviral treatment (ART), she presented with diarrhea, a low CD₄ cell count (10 /µL) and Salmonella bacteremia. She remained febrile despite antibiotic treatment. After re-initiation of ART her pancytopenia worsened and extreme hyperbilirubinemia (max. 495 µmol/L) developed. Immune reconstitution inflammatory syndrome was considered and steroids were started. Her plasma EBV-load was high (2x10⁵ IU/ml) but lymphoproliferative disease could not be proven at that stage. Hemophagocytic lymphohistiocytosis (HLH) was suspected, although some typical markers like low fibrinogen and hypertriglyceridemia were absent. She developed progressive ascites, coagulopathy and hyperferritinemia (max. 8567 µg/l). Despite treatment with rituximab, dexamethasone, interleukin-1 receptor antagonist and broad-spectrum antibiotics she died 26 days after her initial presentation. Bone marrow biopsy confirmed the diagnosis of HLH and revealed Hodgkin’s disease.

Background: HLH is a rare but life-threatening syndrome of excessive immune activation, characterized by overly activated lymphocytes and macrophages causing a storm of cytokines and phagocytosis of blood cells. Primary HLH is a genetic disorder, generally affecting children. Secondary HLH can be triggered by infections (especially EBV), hematological and other malignancies, and auto-immune disorders. The presence of hyperbilirubinemia in patients with HLH is an adverse prognostic factor.

Clinical relevance: This case underlines the broad differential diagnosis of persistent fever and laboratory abnormalities in patients with AIDS. In addition, although HLH was rightly suspected, this patient lacked some of its key laboratory and clinical markers, exemplifying the protean manifestations and challenging diagnosis of this dramatic clinical syndrome.
Successful treatment of chronic hepatitis E infection with pegylated-interferon-alpha in a immunodeficient patient with ribavirin treatment failure

R.A. Mousset, M.G.A. Van Vonderen, A. Al Moujahid
'Medisch Centrum Leeuwarden, Afdeling Interne Geneeskunde, Leeuwarden

Case: A 51-year-old patient with relapsed chronic lymphocytic leukemia (CLL) was diagnosed with acute hepatitis E virus (HEV)-infection. Spontaneous clearance was not achieved. After an initial response with undetectable serum HEV RNA, ribavirin was continued during chemoimmunotherapy because of persistent positive stool HEV RNA. After 8 months of oral ribavirin the HEV relapsed. Sequence analysis revealed two HEV RNA mutations (D1384N and G1634R) associated with ribavirin treatment failure. Pegylated-interferon-alpha therapy was initiated first for 6 weeks and later for 3 months, both times followed by clinical and virological relapse. Eventually HEV clearance occurred after 8 months continuous therapy with pegylated-interferon-alpha. HEV viral load remained undetectable in serum and stool samples thereafter.

Discussion: HEV is one of the most common causes of acute hepatitis worldwide. Although acute HEV infections are often asymptomatic and self-limiting, immunosuppressed patients are at risk for developing chronic hepatitis, which may potentially lead to cirrhosis and liver failure. Antiviral therapy with ribavirin should be considered as treatment of choice for patients who fail to achieve viral clearance after reducing immunosuppression. Ribavirin treatment failure can occur which has been associated with several mutations in the HEV RNA genome.

Conclusion: As illustrated in our case, pegylated-interferon-alpha can be an effective treatment in patients with chronic HEV infection and ribavirin treatment failure. Treatment duration should be determined by HEV viral load in serum and stool samples.
A patient with fever and skin lesions after vacation in South Africa

M.W.L. van Geffen, J.M. van Niekerk, D. Posthouwer
Maastricht Universitair Medisch Centrum, Afdeling Interne Geneeskunde, Maastricht

A 61-year-old patient presented with fever started six days after she returned from a four-week vacation in South Africa. The patient complained of mild headache and localised myalgia in her lower back. Furthermore a vesicular and maculopapular rash was seen on both legs. One skin lesion showed a central necrotic core. The laboratory showed an elevated CRP (40 mg/l), the other laboratory results were unremarkable.

Considering a Rickettsial infection because of the specific skin lesion, also known as an eschar, we prescribed doxycycline. Serological testing was performed. The fever disappeared 48 hours after starting antibiotic treatment and the skin lesions improved rapidly. The early phase indirect immunofluorescent assay was negative. Repeat serology after 10 days showed a clear serum conversion, confirming the diagnosis of a Rickettsial infection most probably due to African tick bite fever considering the travel history.

Rickettsiae are gram-negative bacteria divided into several bio-groups. African tick bite fever of the spotted fever group is caused by *R. africae* and generally transmitted by ticks. Serology typically shows an elevated IgG/IgM antibody titre. African tick bite fever represents 87% of all Rickettsial infections. With an incubation period of 5-10 days African tick bite fever is often seen in travellers from South Africa. The symptoms are self-limiting within 10 days in most patients. Rash due to Rickettsial infections is quite common and may present as a macular or maculopapular rash and even with a single or multiple eschar(s). Start early antibiotic treatment with Doxycycline to reduce the duration of symptoms.
Tetanus after inadequate post-exposition prophylaxis in an unvaccinated patient

D.A. Lionarons, J.G. Röttgering, D. Herderscheê, P.J. de Vries
Tergooi, Afdeling Interne Geneeskunde, Hilversum

Case: An 83-year-old male was admitted to the Cardiac Care Unit with progressive pain of the left arm and jaw since 3 days. A week prior he had fallen in the garden and a laceration of his left arm was treated at the emergency room. It was unclear if he had been immunised against tetanus at the emergency room or as a child. Physical examination showed a closing wound on the left arm, spasms of the left arm, lockjaw and spasms of the facial musculature (risus sardonicus). The clinical diagnosis tetanus was made. The wound was opened and he was treated with tetanus immunoglobulins, metronidazole, diazepam and supportive care. The spasms and pain slowly subsided and after 16 days he was discharged and subsequently immunised. At follow-up 3 months after presentation he was free of symptoms.

Discussion: Clostridium tetani is a gram-positive, anaerobe bacterium that forms spores, which can be found in soil and the gastrointestinal tract of animals. When C. tetani inoculates a wound, it grows and produces a toxin that suppresses release of the inhibitory neurotransmitter GABA, causing muscle spasms. When left untreated, generalised tetanus with autonomic dysfunction and respiratory failure can develop. Unvaccinated patients that might be exposed to C. tetani should be treated with tetanus immunoglobulins and immunised using inactivated toxins. Especially elderly patients are often not adequately vaccinated.

Conclusion: To prevent tetanus, immunisation should always be considered after potential exposure, especially in elderly patients that have not been included in the national vaccination program.
Two cases of HHV-6 encephalitis after stem cell transplantation

L.B. Vrolijk, S.M. Arend, A.C.T.M. Vossen, L.G. Visser
LUMC, Afdeling Interne geneeskunde - Infectieziekten, Leiden

Two patients with a rare cause of encephalitis were diagnosed within four weeks. A 30-y-old man presented with convulsions on day 21 after a double-cord stem cell transplantation (SCT) for acute myeloid leukemia (AML), while still pancytopenic and on ciclosporin. After recovering from the convulsions and treatment of low serum sodium he remained encephalopathic. The cerebrospinal fluid (CSF) showed a normal cell count, protein and glucose but an MRI scan of the brain showed diffuse T2 hyperintensity and diffusion-restriction.

A 41-y-old woman presented with acute amnesia six weeks after an unrelated allogeneic SCT for AML with fair recovery of blood cells. Because of HLA-DR mismatch (9/10) she received ciclosporin as graft-versus-host prophylaxis. The day before presentation she had complained of headache and seeing flashing lights. The leukocyte count and differential were normal. The CSF showed a normal cell count, protein and glucose. An MRI showed mild leukoaraiosis, but no other abnormalities. In both patients the PCR of CSF was positive for human herpesvirus 6 (HHV-6), and both were treated with ganciclovir. After four weeks of ganciclovir, the first patient had good recovery, however with some memory defects. The clinical course of the second patient, who is still on treatment, will be reported at the ‘Internistendagen’.

HHV-6 encephalitis after SCT, which occurs in 0-11.6% of patients, is caused by reactivation of HHV-6. Antegrade amnesia is a characteristic symptom and should prompt diagnostic tests for HHV-6 as an early diagnosis is likely to improve the outcome.
A 68-year-old Dutch man presented to the Emergency Department with fever, papular rash and arthralgia. He recently travelled to Australia, where he stayed for approximately one month in the surroundings of Melbourne and Sydney. He had an adventurous holiday, including rock-climbing and hiking. He had been frequently bitten by mosquitoes despite the use of DEET. Four days after his return to the Netherlands he developed a fever. The next day he complained about an itchy papular rash and arthralgia of his hands and right knee. One day later he presented at the ER, where his physical examination revealed a papular rash covering his entire body. There was no lymphadenopathy and besides a slightly warm knee there were no other signs of arthritis. He had a normal body temperature of 37.6°C. Laboratory findings showed thrombocytopenia (136 x 10^9/l), normal leukocytes (5.88 x 10^9/l), a creatinine level of 104 umol/l and an elevated C-reactive protein (CRP) (46 mg/L). Based on this clinical presentation and his travel history, Ross River Virus (RRV) was a suspected cause. Serology showed the presence of IgM in the initial serum, followed by a rise in IgM titre and seroconversion for IgG antibodies specific for RRV two weeks later. He was treated with analgetics and fully recovered.

This case report serves to create awareness among physicians to consider travel-related RRV disease in patients with fever, arthralgia and rash returning from the New South Wales region in Australia, especially since the recurrent outbreaks of RVV the past years.
More targeted use of oseltamivir and in-hospital isolation facilities after the implementation of a rapid molecular diagnostic panel for respiratory viruses in immunocompromised adult patients

UMC Utrecht, Afdeling Interne Geneeskunde/Infeczieziekten, Utrecht

Background: Immunocompromised adults are more vulnerable to a complicated course of viral respiratory tract infections (RTI) needing hospitalisation. Evidence on the effect of implementation of rapid molecular diagnostics for viruses on use of in-hospital isolation facilities, oseltamivir and antibiotic usage, and other clinical outcomes in immunocompromised patients, is lacking.

Methods: A before-after study during two consecutive respiratory viral seasons, including immunocompromised adult patients presenting at a tertiary care emergency department with clinical suspicion of RTI. During the first season (2016/2017), respiratory viruses were detected using in-house real-time PCR. The second season (2017/2018), we implemented a diagnostic flowchart including a rapid molecular test for 15 respiratory viruses (FilmArray®). We assessed the effect of this implementation on need for isolation, antivirals and empirical antibiotics.

Results: We included 192 immunocompromised adult patients during the first and 378 during the second season. Respiratory viral testing was performed in 135 patients (70%) during the first and 284 (75%) during the second season (p = 0.218) of which 213 (75%) using the rapid test. After implementation, use of in-hospital isolation facilities was reduced (adjusted odds ratio 0.35, 95%CI 0.19-0.64). Furthermore, adequate use of oseltamivir improved, with fewer prescriptions in influenza negative patients (0.15, 95%CI 0.08-0.28) and more in influenza positive patients (11.13, 95%CI 1.75-70.86). No effect was observed on empirical antibiotic use, hospital admissions, length of hospital stay or safety outcomes.

Conclusions: Implementation of rapid molecular testing for respiratory viruses in adult immunocompromised patients results in more adequate use of oseltamivir and in-hospital isolation facilities without compromising safety.
Acute monocytic myeloid leukemia complicated by tumor lysis, renal failure and respiratory distress: thoughts on CVVH

J.K. Humalda, F. Waanders, H. Kieft, G.L. van Sluis
Isala, Department of Internal Medicine, Zwolle

A 49-years old male patient was referred to our hospital for treatment of acute myeloid leukemia. He was analyzed elsewhere because of fever of unknown origin with inconclusive PET-scan and bone marrow biopsies. The previous weeks he developed bone pain, thrombocytopenia and shortness of breath. At admission there was marked leukocytosis (128.1 x10^9/L), evidence for spontaneous tumor lysis syndrome (TLS) with high uric acid (0.88 mmol/L) and LDH (3110 U/L), together with acute renal failure (creatinine 265 µmol/L). Peripheral blood flowcytometry demonstrated blasts and (pro) monocytes, indicative of acute monocytic myeloid leukemia (classification pending); cytarabine/idarubicin was initiated immediately. TLS was treated with hyperhydration and rasburicase 3mg twice daily. Uric acid dropped to 0.09 mmol/L. The next 3 days he had progressive dyspnea accumulating in an ICU admission on the fourth day. Chest-radiographs demonstrated progressive pleural effusion. With Optiflow (50 L/min, FiO2 0.70) oxygen saturation was 90%. Despite escalating doses of furosemide, diuresis did not increase. Uric acid rose to 0.67 mmol/L, creatinine to 405 µmol/L, and phosphate to 3.12 mmol/L. We (intensivist, nephrologist, hematologist) discussed initiation of CVVH. CVVH would facilitate uric acid and phosphate removal, and reduce pleural effusion. However, adverse effects include bleeding, infection, and reduction of renal perfusion which could provoke deposition of uric acid and further loss of renal function. We would like to share our thoughts about this dilemma and report the effect of CVVH 4L/h, without fluid removal, in adjunct to rasburicase for the treatment of TLS complicated by acute renal failure and pleural effusions.
The triad of diabetic ketoacidosis, severe hypertriglyceridemia and pancreatitis in de novo diabetes

J. Tuin, N. Josephus Jitta, T.h.F. Veneman
ZGT, Afdeling Interne Geneeskunde, Almelo

The triad of diabetic ketoacidosis (DKA), hypertriglyceridemia (HT) and acute pancreatitis (AP) is a rare phenomenon, with a high mortality-rate. We describe a case of de novo type 2 diabetes complicated by this triad.

A 40-year-old man presented at the Emergency Department with disorientation, dyspnea, and thirst. Physical examination showed a BMI of 35 and an increased breathing-frequency. Laboratory results showed CRP 259, lipase > 600 U/L, a metabolic acidosis (pH of 6.94, bicarbonate 4 mmol/L) and triglycerides 41.2 mmol/L. HbA1c was increased, and anti-GAD was negative consistent with DM2. A Cat-scan showed an AP.

DKA in DM2 and AP were treated with insulin and fluid therapy. The patient did not experience abdominal discomfort. After 6 days the patient could be transferred to the internal ward in good condition. Hypertriglyceridemia improved without specific treatment. With a basal-bolus regimen the DM2 was well controlled.

We hypothesized that the patient had developed DM2 long before presentation, resulting in DKA due to a suspected infection. Consecutively, the DKA caused HT, which consequently caused AP, resulting in an even more serious lack of insulin, thereby causing further deterioration.

It is important to ascertain the presence of AP in DKA because it has clinical implications: more aggressive volume-repletion and tighter glucose-regulation is needed. Moreover, the presence of AP in DKA deteriorates the prognosis. AP in DKA can result in a systemic inflammatory response syndrome (SIRS) and multi-organ failure with a lethal course. Therefore, swift recognition and adequate treatment of this rare triad is urgently required.
Acute-on-chronic lithium intoxication

R.M. Nieuwenhuize, L. Dawson
Reinier de Graaf Gasthuis, Afdeling Intensive Care, Delft

Case: A 68-year old female, known with bipolar disorder treated with 400 mg lithium daily (Priadel, slow-release), presented herself, without symptoms, 30 minutes after ingestion of 12,000 mg lithium. She was treated by gastric lavage, intravenous hydration and admitted to the ICU. The lithium level at admission was 2.44 mmol/l (therapeutic range: 0.6-0.8 mmol/l) but nevertheless raised 8 hours later to 6.97 mmol/l. With hemodialysis during 4 hours the lithium level dropped till 1.96 mmol/l but 1 hour later, the lithium level increased to 2.3 mmol/l after which CVVH was started during 48 hours. Thereafter the lithium level remained low.

Discussion: This case shows the importance to recognize the differences between two different intentional auto-intoxications with lithium: the acute intoxication (in patients naïve to lithium) and the acute-on-chronic intoxication (in patients on chronic lithium usage). Half-life elimination time of lithium is prolonged in patients on chronic lithium usage since lithium is stored, partly intracellularly. In acute intoxication, lithium will not be able to distribute to these tissues and toxicity is mostly mild. In acute-on-chronic intoxication, the intracellular spaces will already contain lithium so a smaller amount of lithium can cause severe toxicity. When on dialysis, the extracellular concentration will descend, creating a concentration gradient and causing lithium to move to extracellular. However, hemodialysis removes lithium quicker from the extracellular compartment than lithium can move from the intracellular compartment, causing the plasma level to raise again after hemodialysis is discontinued.

Conclusion: In acute-on-chronic lithium intoxication, a strong rebound effect might occur.
Concomitant periarteritis nodosa and complement factor H deficiency in a patient with acute renal failure and adenocarcinoma of the lung

N.E. Tibben, R.M.L. Brouwer
MST, Afdeling Interne geneeskunde, Enschede

Case: A 65-year-old female presented with acute kidney injury (AKI). Serum creatinine (sCr) was 549 \( \mu \)mol/l, haemoglobin 5.8 mmol/l (n > 7.5 mmol/l), platelet count 132 10^9/l (n = 150-400), and LDH 779 U/l (n < 250). Peripheral blood smear showed schistocytes (++). ANA and ANCA screening were negative. Complement factor C3 was 0.6 g/l (n = 0.9-1.8 g/l). Haptoglobin was 1.7 g/l (n = 0.3-2 g/l). A tentative diagnosis of acute renal failure (AKI) secondary to thrombotic microangiopathy (TMA) was made and plasma exchange therapy (PLEX) and dialysis (HD) were immediately initiated. ADAMTS-13 activity was 63% (normal). No Shiga toxin producing E.Coli was found. Complement factor H (CFH) was 53 ug/ml (n: 122-315 ug/ml) and a CFH auto-antibody was detected (> 415 AU/ml). Renal biopsy showed necrotizing vasculitis of middle sized vessels and no TMA lesions. A diagnosis of polyarteritis nodosa (PAN) was made. PLEX was stopped and treatment with high dose steroids was started. An adenocarcinoma of the lung was treated with radiotherapy. Renal function gradually improved and HD was stopped after 2 months. Recent sCr is 112 \( \mu \)mol/l. CFH levels returned to normal and CFH auto-antibody level decreased below detection level. PCR and DNA sequence analysis did not show an abnormal gene related to complement mediated kidney disease. CFH function screening was normal.

Conclusion: We report a patient with laboratory results compatible with TMA/aHUS and a kidney biopsy with PAN and no TMA lesions who was successfully treated with PLEX and steroids. CFH auto-antibodies are associated with early stage NSCLC and induce low CFH concentration without full blown aHus.
Staphylococcus-associated glomerulonephritis: a clinical diagnosis

S.J.W. van Kraaij, G.A.J. van Boekel, S.J.J. Logtenberg
Diakonessenhuis, Afdeling Interne Geneeskunde, Utrecht

Case: A 69-year old woman without relevant medical history was admitted to our hospital with coughing, fever and confusion. Thoracic x-ray revealed bilateral infiltrates. When blood cultures showed *S. aureus*, antibiotic treatment was switched to intravenous flucloxacillin. During admission, creatinine rose to 436 umol/L and patient developed generalized edema. Acute tubular necrosis was considered, however urinalysis showed gross hematuria and proteinuria (2.5 g/L). ANCA and anti-GBM were negative and C3 and C4 were normal. Despite the latter, the diagnosis ‘staphylococcal-associated glomerulonephritis’ (SAGN) was made.

With antibiotics and supportive care she slowly recovered from the pneumonia. From day 15 after admission kidney function recovered as well. At discharge on day 27 creatinine was almost back at her baseline level (126 umol/L).

Discussion: SAGN is a rare complication of active *S. aureus* infection caused by glomerular depositions of immune complexes formed from circulating *S. aureus* antigen and host antibodies. SAGN can mimic primary IgA nephropathy with IgA dominant immunofluorescence staining on kidney biopsy. Treatment consists of removing the causative pathogen and supportive care. Only when the active infection is properly treated and the glomerular disease is not improving, immunosuppressive therapy should be considered. A kidney biopsy is strongly advised at that point.

Conclusion: In patients with active *S. aureus* infection and concomitant glomerulonephritis without likely alternative causes, the need for biopsy at the acute stage is obviated due to the high clinical likelihood of SAGN. SAGN will often resolve with adequate treatment of the bacterial infection.
Introduction: Literature describing bisphosphonate-induced nephropathy is conflicting. Cases: Two patients (71 and 82) were treated for prostate carcinoma with osseous metastases with intravenous zoledronic acid. Serum creatinin of these patients increased (104-2177 and 90-170 µmol/L) after their third and fifth bisphosphonate administration, respectively. Renal biopsies showed signs of acute tubular injury, one with vacuolization of the tubular epithelia cells (TEC) and one with signs of TEC apoptosis. No signs of primary glomerular disease were found. One patient became dialysis dependent despite cessation, whereas renal function normalized within two months in the other. Third, creatinin of a woman (60), treated with zoledronic acid for osseous metastases of a mamma carcinoma, increased from 54 to 142 and decreased to 75 µmol/L after cessation. Renal biopsy showed identical findings to the second case. Lastly, a woman (77) with polymyalgia rheumatica was prescribed zoledronic acid intravenously for a fracture within 1 year after start of oral risedronate. Within three weeks, her creatinin rose from 105 to 613 µmol/L. No renal biopsy was performed, but creatinin returned to baseline after cessation.

Discussion: In rat studies and human case reports, bisphosphonates induced tubular damage comparable to the findings described above. In literature, zoledronic acid appears to be involved more frequently in causing renal damage when compared to other bisphosphonates.

Conclusion: Although highly effective in preventing complications in patients with osseous metastases and in preventing fractures, bisphosphonates may induce acute tubular injury. Creatinin levels should be checked regularly in these patients, especially when intravenous therapy is prescribed.
A Cold Case: Monoclonal Gammopathy of Cutaneous Significance

T.S. Schoot¹, M.C. Minnema², J.J. Beutler¹
¹Jeroen Bosch Ziekenhuis, Afdeling Nefrologie, ’s-Hertogenbosch, ²UMC Utrecht, Afdeling Hematologie, Utrecht

Case: An 83-year old patient presented with renal insufficiency, nephrotic-range proteinuria (8.20 g/24 hr) and skin lesions. Within seven months, the eGFR had gradually decreased from 64 to 16 ml/min/1.73 m² and the skin lesions had progressed from episodic purpura on the legs to permanent palpable purpura on trunk and all extremities. Laboratory investigations revealed monoclonal free light chain type kappa of 170 mg/L (reference: 6.70-22.40 mg/L) with a kappa/lambda light chain ratio of 3.1 (reference: 0.31-1.56), presence of cryoglobulins (monoclonal IgM kappa and polyclonal IgG and IgA) and low complement C3 and C4. Hepatitis C serology was negative. Bone marrow examination revealed 1% monoclonal B-cells. Furthermore, kidney biopsy showed glomerulonephritis with deposition of IgM, kappa and C3 and skin biopsy showed leukoclastic vasculitis with deposition of C3 in the vascular wall.

Diagnosis: Skin vasculitis and renal insufficiency caused by cryoglobulinemia secondary to monoclonal gammopathy, i.e. monoclonal gammopathy of cutaneous and renal significance (respectively MGCS and MGRS).

Management: Treatment with prednisone (initially 60mg per day) had a spectacular response. After only 2.5 weeks, the skin lesions had vanished and eGFR had improved to 45 ml/min/1.73m². Furthermore, cryoglobulins were no longer detectable and kappa/lambda light chain ratio normalized. Three months later, the patient is still in remission.

Clinical relevance: Although recognition of MGRS has improved, cryoglobulinemia and dermal involvement (MGCS) are less well-known manifestations of MGUS. Early identification of MGCS-related skin lesions will diminish diagnostic delay and thus improve treatment outcome of organ damage caused by MGUS (for example MGRS and MGCS).
Secondary hyperoxaluria due to pancreatic insufficiency

D.G.L. de Martines, S. Gianotten, W.A.G. van der Meijden, J.F.M. Wetzels
Radboudumc, Afdeling Nierziekten, Nijmegen

A 64-year-old male with a history of type 2 diabetes and exocrine pancreas insufficiency due to chronic alcohol abuse, was referred for dialysis following acute renal insufficiency. Two months prior, the patient had started a proton-pump-inhibitor for gastro-esophageal reflux. When his serum creatinine increased from 50 to 222 µmol/l, a tubulo-interstitial nephritis was suspected. The PPI was ceased and the patient started taking prednisone. However, his renal function continued to deteriorate.

Upon presentation in our hospital, serum creatinine had increased to 742 µmol/l. Serologic evaluation was negative, and urinalysis revealed leukocyturia and mild erytrocyturia. Renal ultrasound showed no hydronephrosis. A renal biopsy was performed, revealing tubulopathy and oxalate crystal depositions, proving the diagnosis of oxalate nephropathy. This was confirmed by an elevated serum oxalate: 116.9 µmol/l (reference value < 5 µmol/l).

Oxalate nephropathy is associated with exocrine pancreas insufficiency, gastric and pancreatic surgery and inflammatory bowel disease. Normally, dietary calcium binds oxalate to form calciumoxalate, which is excreted in the stool. In pancreatic insufficiency, fatty acids bind calcium instead, allowing oxalate to be absorbed in the colon. The resulting hyperoxaluria can cause renal insufficiency. Progression may be accelerated by an acute event, such as dehydration.

In our patient, hemodialysis, restricting oxalate intake, prescribing calcium with meals and cholestyramine reduced serum oxalate levels and resulted in a partial recovery of renal function (serum creatinine 325 µmol/l) without dialysis dependency.

Conclusion: Secondary hyperoxaluria is often unrecognized and should be considered in patients with a medical history of pancreatic insufficiency and progressive kidney injury.
A 55-year-old female was referred to the haematology department for analysis of a 4 cm inguinal mass. Her medical history reported excision of an inguinal inflammatory pseudotumor in 2016. She reported fatigue and mild edema of the feet. Needle biopsies displayed a recurrent inflammatory pseudotumor that could be IgG4-related as > 50% of IgG plasma cells were positive for IgG4 (IgG4-staining was not performed in 2016). Further work-up yielded findings consistent with IgG4-related disease (IgG4-RD) such as mild eosinophilia, plasma IgG4 3.31 g/L (0.080-1.40) and IgE 8900 U/mL. Notably, a decline of eGFR (50 ml/L vs. > 90 in 2016) and albumin of 29 g/L raised concern for possible renal involvement. The protein level in 24-hour urine was 4.3 g/L. To confirm the suspicion of IgG4-RD nephrotic syndrome and renal insufficiency, a renal biopsy was performed. This revealed an advanced stage of secondary membranous nephropathy, but no tubulointerstitial inflammation and mainly IgG3 depositions. As serological tests for other causes of nephrotic syndrome were negative, she was considered to have IgG4-RD renal involvement and is currently treated with prednisone.

**Discussion:** Although the most common presentation of IgG4-related renal disease is tubulo-interstitial nephritis, membranous glomerulonephritis has also been described. In IgG4-RD membranous nephropathy, IgG4 deposition is usually, but not always predominant on the glomerular basement membrane and concurs with other types of IgG.

**Conclusion:** This case supports the finding that IgG4-RD may underly a nephrotic syndrome with renal insufficiency, even without the classical findings of TIN or IgG4 depositions in the renal biopsy.
Case: A 27-year old Caucasian female, with morbid obesity (BMI 67) and Hashimoto’s disease, had a coincidental finding of an elevated sedimentation rate. Analysis showed a nephrotic range proteinuria (4.3 g/24 hours) with normal kidney function. Due to her BMI, kidney biopsy could not be performed for a long time. Her proteinuria was considered to be a form of focal segmental glomerulosclerosis due to severe obesity. Diabetes mellitus was excluded. An angiotensin blocker and salt-restriction were started, she was advised to lose weight. Over the years proteinuria did not dissolve and kidney function diminished slowly. Twelve years later she underwent gastric bypass. Despite massive weight loss (BMI 34) her proteinuria did not improve. Kidney biopsy was performed and revealed both fibrillary glomerulonephritis and oxalosis or calcinosis.

Fibrillary glomerulonephritis is a form of nonamyloid glomerulonephritis and an uncommon cause of glomerular disease. It results from deposits derived from immunoglobulins. Fibrillary glomerulonephritis was used to be considered an idiopathic disorder. However, approximately 30% of patients have a history of malignancy, monoclonal gammopathy, or autoimmune disease. In our patient Hashimoto’s disease was present; analysis for M-protein, IgG subclasses, cryoglobulines, serology for Hepatitis C was negative.

The result of the analysis of calcinosis and oxalosis is not available yet. Hyperoxaluria is related to malabsorption and reported in gastric bypass patients.

Conclusion: This case report presents a rare cause of glomerulonephritis. It supports the clinical importance of performing a kidney biopsy. However, morbid obesity causes diagnostic challenges in the clinical work-up of proteinuria.
Diuretic induced hypophosphatemia

N.E. Tibben, H.S. Brink
MST, Afdeling Interne Geneeskunde, Enschede

Case: A 49-year-old woman with a history of factor V Leiden was presented with hypophosphatemia 0.65 mmol/l (n = 0.9-1.5 mmol/l). The hypophosphatemia was diagnosed during a routine blood test performed by the general practitioner. She had no complaints, a normal diet, and consumed no alcohol. She used hydrochlorothiazide for several years, because of peripheral oedema. There was no hyperparathyroidism, and no vitamin D deficiency. We related the hypophosphatemia to the hydrochlorothiazide, which was then stopped. The phosphate levels normalized, but the oedema returned. We switched to furosemide, choosing a loop diuretic because of the different mode of action at a different part of the renal tubules. After four weeks, phosphate levels again dropped to 0.56 mmol/l. We switched treatment to bumetanide at an equipotent dose as the furosemide, thereafter the phosphate levels returned to normal values.

Discussion: In literature we found that thiazide diuretics can cause hypophosphatemia as a rare side-effect. However a switch to furosemide did not solve the problem, despite different sites of action in the renal tubule. The underlying mechanism is not entirely clear, but may be the result of increased renal phosphate loss through inhibition of carbonic anhydrase. The mechanism by which carbonic anhydrase inhibition can cause phosphate loss is not fully understood. Both hydrochlorothiazide and furosemide are weak carbonic anhydrase inhibitors, where bumetanide is not.

Conclusion: Hypophosphatemia can be a side-effect of thiazide diuretic use. When diuretic therapy is needed, substitution by furosemide does not solve this problem.
Performance and pitfalls of the fresenius? body composition monitor for water balance management in patients on hemodialysis

J.M. Schotman¹, M.M.G.J. van Borren¹, J.F.M. Wetzels², H.J. Kloke³, L.J.M. Reichert¹, H. de Boer¹
¹Ziekenhuis Rijnstate, Afdeling Interne Geneeskunde, Arnhem,
²Radboud UMC, Afdeling Nefrologie, Nijmegen

Introduction: The multi-frequency body composition monitor (BCM, Fresenius®) has been developed as a tool to assess the volume of fluid overload (FO) in patients on hemodialysis (HD) to improve guidance of ultrafiltration (UF). The aim of this study was to assess the accuracy of the BCM.

Methods: The BCM measures resistance and reactance at 50 frequencies between 5 and 1000 kHz and calculates FO volume by an algorithm including height, weight, and intra- and extracellular resistance. The reproducibility of BCM measurements was investigated in 16 patients. The accuracy of estimating changes in FO was examined by comparing the BCM predicted volume changes (ΔFO) with actually measured ultrafiltration volumes (UFV) in 24 patients during conventional HD.

Results: The discrepancies between ΔFO and UFV ranged from -0.8 to 1.4 L. The poor performance of the BCM was partially explained by the limited reproducibility of reactance measurements at frequencies > 200 kHz. This induced a mean error in the FO estimate of 0.24 ± 0.03 L, but this may increase to 0.5 L in individual patients. The lowest variation was found at 50 kHz.

Conclusion: The BCM is not sufficiently accurate to estimate UF volumes in individual patients on HD. This can be partly explained by limited reproducibility of the BCM. Other possible error sources are assumptions in calculation algorithm, posture dependent redistribution of fluid, and diffusion of electrolytes. Accuracy may be improved by measurements at a single frequency of 50 kHz only.
Delayed onset of severe hypercalcemia in a patient with rhabdomyolysis-induced acute kidney injury

S.R.K. Malahé, A.D.O. Hensen, D. Soonawala
Hagaziekenhuis, Department of Internal Medicine, The Hague

Background: In a third of patients with rhabdomyolysis-induced acute kidney injury, a biphasic plasma calcium profile can occur, sometimes causing late-onset hypercalcemia.

Case: A 70-year-old woman with a history of schizophrenia was found at home, lying on the ground. She was admitted to the hospital because of rhabdomyolysis-induced acute kidney injury (CK 128005 U/L, ASAT 1370 U/L, LD 3911 U/L, creatinine 213 umol/L, eGFR CKD-EPI 20 mL/min/1.73 m²). Despite prompt intravenous rehydration, she remained oliguric and developed edema. At day three, haemodialysis was initiated. At presentation she had a normal serum calcium (2.15 mmol/L, corrected for albumin). At day 11, she was no longer oliguric and haemodialysis was stopped. At day 15, she started to develop progressive hypercalcemia during the polyuric phase of recovery. Her serum calcium increased to 3.37 mmol/L (ionized calcium 1.55 mmol/L) at day 18, with serum phosphate at 2.20 mmol/L, suppressed parathyroid hormone (2.0 pmol/L), a level of low vitamin D (25 nmol/L) and no M-protein. Except for constipation, she had no complaints. The QTc-interval was 424 ms. Dialysis against low calcium in the dialysate was started and she received pamidronic acid and saline infusion. Her serum calcium quickly normalized and remained normal from day 19 onwards. Currently her eGFR is 35 mL/min/1.73 m².

Conclusion: Severe hypercalcemia can complicate the recovery after rhabdomyolysis-induced acute kidney injury. Mobilization of calcium from calcium phosphate deposits in injured muscles is the proposed mechanism of the biphasic calcium profile. Prolonged monitoring of serum calcium should be performed.
Treatment of tubulointerstitial nephritis in Sjögren’s syndrome with cyclophosphamide: a case-report

S.E. van Roeden¹, T.J. Tobe¹, C.A. Stegeman²

¹Diakonessenhuis Utrecht, Afdeling Interne Geneeskunde, Utrecht, ²UMCG, Afdeling Nefrologie, Groningen

A 57-year old female patient with Sjögren’s syndrome presented with a gradual reduction in renal function over years (serum creatinine 137 µmol/l, eGFR 37 ml/min/1.73 m²). The urinary sediment was normal, proteinuria absent. Renal biopsy demonstrated extensive lymphocytic infiltration of the tubulointerstitium. Tubulointerstitial nephritis as part of Sjögren syndrome was diagnosed. Oral prednisone 60 mg (0.9 mg/kg) once daily was initiated without improvement in renal function after three months. Oral cyclophosphamide 150 mg (2.1 mg/kg) once daily was added, resulting in an improvement in renal function. Following three months of cyclophosphamide, therapy was changed to azathioprine 100 mg once daily and continued as maintenance therapy. Prednisone was tapered and stopped. During follow-up (14 months since start of cyclophosphamide) renal function remained stable (serum creatinine 98 µmol/l, eGFR 55 ml/min/1.73 m²). Tubulointerstitial nephritis (TIN) is the most common manifestation of renal Sjögren’s syndrome and usually mild with minimal loss of renal function. Treatment of TIN in pSS is primarily with high-dose glucocorticoids. However, our patient did not respond to treatment with glucocorticoids. In literature, we found three articles reporting 17 patients with TIN in pSS with cyclophosphamide. In three case-reports, renal function stabilized in two and improved in one patient. In one retrospective cohort study, 14 patients treated with cyclophosphamide and glucocorticoids responded better (in terms of improvement of eGFR) compared to 56 patients treated with glucocorticoids only. In conclusion, in patients with TIN with renal function loss in pSS not responding to high dose glucocorticoids, cyclophosphamide is a treatment option.
Linking weight loss and hypoalbuminemia in a patient with malignant pleural mesothelioma

L.M.J. Wijnands, M. Smeekens, J. Verhave, E. Ruijter, N. Claessens
Rijnstate, Afdeling Interne Geneeskunde, Arnhem

Introduction: Patients presenting with weight loss may have hypoalbuminemia secondary to the underlying disease and poor intake. However, recognizing nephrotic syndrome helps to find diagnostic clues.

Case: A 79-year old men presented with progressive weight loss, fatigue and a medical history of a recent pneumonia. He was normotensive and had peripheral edema. Further examination revealed ascites, nephrotic syndrome (proteinuria 9 g/24 h) and fludeoxyglucose F 18 (FDG)-avid pleural thickening on the right side. The ascites was transudative with elevated triglycerides (3.9 mmol/l), without malignant cells. Negative Anti-PLA2R antibodies made primary membranous nephropathy an unlikely cause of the nephrotic syndrome. Kidney biopsy revealed no significant lesions and immunofluorescence and Congo stain were negative (which made minimal change nephropathy the most likely cause). The clinical condition of the patient worsened. Eventually, we weighted the surgical risks in his poor physical state and a diagnostic video assisted thoracic surgery (VATS) with pleural biopsy was performed. Pleural biopsy revealed an epithelioid mesothelioma. Patient died before palliative chemotherapy was started.

Conclusion: Ten percent of the patients with nephrotic syndrome have underlying malignant disease.

1 The renal lesions are most frequently based on membranous nephropathy, due to deposition of circulating immune complexes associated with malignancies.

2 In pleural mesothelioma renal manifestations are extremely rare. A few case reports describe minimal change nephrotic syndrome in mesothelioma patients, caused by mesothelioma cell-derived cytokines.

3-6 We describe a rare cause of nephrotic syndrome associated with mesothelioma. In the workup of weight loss and hypoalbuminemia, urine analysis is indispensable.
A 63-year-old male was hospitalized with an acute kidney failure (AKI; eGFR 15 ml/min/1.73 m²) and hypercalcemia. Since pre- and postrenal causes were excluded, we suggested a renal cause of the AKI. In combination with the elevated serum Calcium (2.97 mmol/L) we considered a multiple myeloma or sarcoidosis, but m-protein in serum and urine was normal and a pulmonary computed tomography (CT) was negative for pulmonary involvement in sarcoidosis. We performed a kidney biopsy which showed extensive tubulointerstitial fibrosis with a plasma-rich infiltrate, mostly an increase of IgG4-positive plasma cells (24 per high-power field) and one possible granuloma was seen. There were no signs of glomerulopathy, immune complex related disease or cast nephropathy. Afterwards we measured serum IgG4 and this was increased (3.29 g/L). We diagnosed patient having an immunoglobulin G4 (IgG4) related disease. Since hypercalcemia is not a known feature of IgG4 related disease, we considered alternative diagnosis for the hypercalcemia, but the patient had no signs of lymphoma, other bone-malignancy, hyperparathyroidism, overuse of vitamin D etcetera. After initiating therapy with corticosteroids, the serum-calcium rapidly normalized. We concluded that the hypercalcemia was secondary to the IgG4 related disease. We tried to explore the mechanism by which IgG4 related disease in this case may have caused hypercalcemia. Serum whole PTH and PTHrP were low. 25-vitaminD was reduced and 1,25- vitaminD was increased. We suggest the possibility that granulomas found in the renal biopsy may be 1,25- vitaminD producing cells, analogue to the mechanism found in sarcoidosis.
A seizure treated with antibiotics

A.C. Fenneman, M.H. Silbermann, S.A. Luykx
Tergooi ziekenhuis, Afdeling Interne Geneeskunde, Hilversum

Case: Presenting a 67-year-old male who was being treated for chronic lymphocytic leukemia and had reached complete remission after treatment with fludarabine. Ten months later, on New Year’s Eve, he presented at our emergency department because of an acute paralysis of the left arm followed by a tonic-clonic epileptic seizure. Apart from slightly elevated inflammation markers, no other abnormalities were found in his laboratory work-up. A CT of the brain revealed a hypodense area in the right frontal lobe. The following day, a gadolinium-enhanced MRI was done, which showed three lesions highly suspicious for a lymphoma or a malignancy and a biopsy was performed. Analysis of the cerebral spinal fluid showed a slight pleocytosis and a reduced CD4/CD8 ratio of 1.0. One day after the biopsy, the patient developed fever and experienced shortness of breath. Broad-spectrum antibiotics were started. Nevertheless, respiratory failure followed and he was admitted to the Intensive Care Unit for assisted ventilation. After further investigation, including a bronchoalveolar lavage (BAL), PCR of the BAL fluid tested positive for *Pneumocystis jirovecii*, a common opportunistic infection. By this time, the results of the brain biopsy revealed a cerebral toxoplasmosis. He was treated with co-trimoxazole intravenously for six weeks and showed a good response with no sign of relapse. Conclusion: With this case we want to emphasize that patients (with CLL) having undergone treatment with chemotherapy like fludarabine, are not only at risk for opportunistic infections during or shortly after chemotherapy, but that there is a persistent increased risk of infection.
Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer; the COLOPEC randomized trial


1OLVG, Afdeling Interne Geneeskunde, Amsterdam, 2Amsterdam UMC – locatie AMC, Afdeling chirurgie

Background: Patients with locally advanced (T4) or perforated colon cancer are at high risk (~25%) of developing peritoneal metastases (PM), often without curative treatment options. In this study, the effectiveness of adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in reducing the development of PM was determined.

Methods: In this multicenter non-blinded superiority trial, patients with c/pT4N0-2M0 or perforated colon cancer were randomized to adjuvant HIPEC followed by routine adjuvant systemic chemotherapy or to adjuvant systemic chemotherapy alone. Adjuvant HIPEC with oxaliplatin (460mg/m², 30 minutes, 42°C, concurrent 5-FU/LV iv) was performed simultaneously (9%) or within 5-8 weeks (91%) after primary tumor resection. In all patients without evidence of recurrent disease at 18 months, a diagnostic laparoscopy was performed. The primary endpoint was PM free survival (PMFS) at 18 months.

Results: Between April 2015 and January 2017, 204 patients were randomized, 102 in each arm. In the control arm, 23 patients were diagnosed with PM, of which 7 by 18 months laparoscopy. In the experimental arm, 19 patients were diagnosed with PM, of which 9 during surgical exploration preceding intentional adjuvant HIPEC, 8 during routine follow-up and 2 by 18 months laparoscopy. In the intention to treat analysis (n = 202), no difference in 18 months PMFS was observed; 76% (control) vs. 81% (experimental), HR 0.86 (0.51-1.45). After HIPEC, 14% of patients developed postoperative complications and encapsulating peritoneal sclerosis occurred in one.

Conclusion: No superiority of adjuvant HIPEC with oxaliplatin could be demonstrated regarding 18 months PMFS in patients with T4 or perforated colon cancer.
Dizziness as a first manifestation of ovarian cancer

M.T.D. Weiland, S.D. Bakker
Zaans Medisch Centrum, Afdeling Interne Geneeskunde, Zaandam

Case: A 76-year old female, with a medical history of benign paroxysmal positional vertigo, visited the Emergency Department with dizziness and nausea since three days. At physical examination we saw a nystagmus, mild dysarthria, subtle ataxia and a tendency to fall. Imaging of the brain showed no acute intracranial pathology, laboratory tests a mild anemia (hemoglobin 7 mmol/l) and elevated Erythrocyte Sedimentation Rate (40 mm/hr). The patient was admitted for observation, during which she told she unintentionally lost 16 kilograms of weight over the last months. Due to the combination of symptoms and laboratory results a paraneoplastic neurological syndrome (PNS) was suspected. A CAT-scan showed abdominal and mediastinal lymphadenopathy, biopsy of an active lymph node revealed an adenocarcinoma originating from the female genital tract. Additional laboratory tests showed a highly elevated CA-125 and high-titer anti-Yo. She was treated with steroids and immunoglobulins, followed by prednison daily. Thereafter, neo-adjuvant chemotherapy for (extra-)ovarian cancer was started (carboplatin-paclitaxel). After a few cycles of chemotherapy her symptoms improved and her lymphadenopathy and CA-125 declined.

Diagnosis: Patient was diagnosed with a paraneoplastic neurological syndrome, more specific paraneoplastic cerebellar degeneration, as a first manifestation of ovarian cancer.

Discussion: In most patients with PNS, the underlying cancer is nog yet diagnosed. Anti-neuronal antibodies can be used as a diagnostic tool, since symptoms are thought to be caused by an autoimmune reaction. Recognition of PNS is important voor early diagnosis and treatment.
The relevance of geriatric assessment for elderly patients receiving palliative chemotherapy

E. van der Vlies¹, S.A. Kurk², J.M.L. Roodhart³, F.L. Gerritse³, P.G. Noordzij¹,
T.C. Pelgrim¹, J.M. Vos³, M. Sohne¹, C.B. Hunting¹, A.M.T. van der Velde⁴, M. Los¹

¹St. Antonius Ziekenhuis, Afdeling Inwendige Ziekten, Nieuwegein, ²UMCU, Afdeling Medische Oncologie, Utrecht, ³Amsterdam UMC – locatie AMC, Afdeling Hematologie, Amsterdam, ⁴Tergooi ziekenhuis, Afdeling Inwendige Ziekten, Hilversum

Background: No tools accurately discriminate between elderly patients who are fit and those who are frail to tolerate systemic palliative treatment. This study evaluates whether domains of geriatric assessment (GA) are associated with increased risk of chemotherapy intolerance in patients who were considered fit to start palliative chemotherapy after clinical evaluation by their treating clinician.

Method: This prospective multicenter study included cancer patients ≥ 70 years who were planned to start first line palliative systemic treatment. Before treatment initiation, patients completed a GA including Activities of Daily Life (ADL), Instrumental Activities of Daily Life (IADL), Mini-Mental State Examination (MMSE), Mini Nutritional Assessment (MNA), Geriatric Depression Scale (GDS-15) and the Timed Up and Go Test (TUGT). The primary endpoint is treatment modification, defined as the inability to complete the first three sessions of systemic treatment as planned. The secondary outcome was treatment related toxicity ≥ grade 3. A logistic regression model, adjusted for clinical relevant confounders was used to determine which tests of the GA were associated with outcomes.

Results: Of the 99 included patients, 47.5% required treatment modifications within 3 cycles. An impaired TUGT was significant associated with treatment modifications (OR 3.1 [1.2-7.9]). In addition, IADL (OR 3.8 [0.7-20.9]) and MNA (OR 2.4 [0.7-3.2]) showed a strong, although not significant, association.

Conclusion: Half of the elderly patients who were considered fit to start palliative systemic chemotherapy required a treatment modification. A short geriatric assessment including TUGT, MNA and IADL may help identify those patients who are at high risk for chemotherapeutic adverse events.
Case: A 67-year-old female patient received adjuvant doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) chemotherapy for early breast cancer. After her first cycle she experienced severe nausea and depression treated with conventional antiemetics and oxazepam.

On day one after cycle two, our patient experienced severe symptoms of somnolence, transpiration, trembling, malaise and nausea. Laboratory studies revealed a hypotonic (253 mOsm/kg) hyponatremia of 118 mmol/l. Serum sodium was 138 mmol/l two days before cycle two. Urinary sodium excretion (129 mmol/l) and osmolality (459 mOsm/kg) were relatively high without concomitant use of diuretics. She was admitted to the Intensive Care Unit and treated with hypertonic saline and fluid restriction. Sodium levels gradually normalized and she recovered without neurological sequelae. Her hyponatremia was attributed to cyclophosphamide and adjuvant treatment was continued with doxorubicin monotherapy uneventfully.

Discussion: Cyclophosphamide is an alkylating agent widely used in antineoplastic and immunosuppressive therapies. Our patient experienced a severe symptomatic hyponatremia due to a rapid onset but temporary cyclophosphamide-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). Drug-induced SIADH develops by stimulating ADH release or accentuating its renal effects, leading to water retention. Following general instructions our patient ensured an ample fluid intake further contributing to her hyponatremia. It is likely that her nausea and psychiatric complaints after cycle one were also caused by an unnoticed hyponatremia.

Conclusion: Cyclophosphamide-induced hyponatremia is a rare but potentially life-threatening complication. Symptoms of hyponatremia and chemotherapy toxicity overlap. This may lead to misdiagnosis or a diagnostic delay with potential major consequences.
Hypercalcemia in endometrial cancer: a bad omen

M.G. Caris, E.H. van der Poest Clement, M.M. Geenen, A.C. Ogilvie
OLVG West, Afdeling Interne Geneeskunde, Amsterdam

Introduction: In endometrial cancer, bone involvement seldom occurs, and hypercalcemia is rare. If hypercalcemia occurs, this is usually caused by humoral hypercalcemia of malignancy, mediated mostly through PTH-rP.

Case: A 52-year-old woman presented to the emergency room with a 1-week history of nausea and vomiting. Laboratory results showed marked hypercalcemia (corrected for albumin): 4.03 (reference 2.15-2.55) mmol/l, normophosphatemia and acute renal failure (creatinine 175 umol/l). PTH and 25-hydroxyvitamin D were normal, ectopic calcitriol production was excluded with low levels of 1,25-dihydroxycholecalciferol. Imaging and biopsy results revealed advanced, high grade endometrial cancer with pulmonary and pelvic bone metastases. PTH-rP was normal. Symptomatic treatment consisted of hyperhydration and zolendronic acid, as well as palliative pelvic radiotherapy. Carboplatin/paclitaxel chemotherapy initially led to normocalcemia and disease stabilization. Unfortunately, the disease quickly progressed with recurrence of hypercalcemia for which she was re-admitted and again received intravenous fluids, zolendronic acid and additional subcutaneous denosumab. Oral calcitonin was started, but unfortunately, this was not tolerated. Despite intensive hypercalcemia treatment and additional liposomal doxorubicin, she developed brain metastases and deteriorated quickly. She was discharged to a hospice within 5 months after diagnosis.

Conclusion: Bone metastases seldom occur in endometrial cancer (only 2% of cases, Int J Gyn Cancer 2014) and do not usually cause hypercalcemia. Our case illustrates that patients can develop symptomatic hypercalcemia due to bone metastases and shows that this is a marker for a poor prognosis in this malignancy.
A rare presentation of metastatic breast cancer

W.R. Kortbeek, M.A.M. Verhoeven, W. Yuen, Q.C. Van Rossum-Schornagel
St. Franciscus Gasthuis & Vlietland, Afdeling Interne Geneeskunde, Rotterdam-Schiedam

Introduction: Lobular carcinoma of the breast is known to metastasize to widely disseminated and unusual sites. We present a patient with metastatic retroperitoneal fibrosis as an extremely rare first sign of recurrent breast cancer.

Case: A 57-year-old female with a history of a cerebrovascular attack and an ypT3N2M0 ER+/PR+/Her2Neu- lobular breast cancer at the age of 54, presented with fatigue and bilateral peripheral edema. Clinical examination showed hypertension. Laboratory tests indicated acute renal insufficiency with creatinin of 202 mmol/L (previously 64 mmol/L) and a normocytary anemia (hemoglobin 6.2 mmol/L, MCV 96 fl). Urine analysis showed an inactive sediment with a normal protein/creatinin ratio and therefore not suspected for a glomular disease. Abdominal ultrasonography reported bilateral hydronephrosis with dilatated urethra.

Based on these findings bilateral double-J stents were inserted in order to restore the renal function. Differential diagnostic was thought of a gynecological post-renal cause, but MRI scanning showed an abnormal soft tissue density surrounding the ureters and the aorta bifurcation suspected for retroperitoneal fibrosis (RPF). A radiological diagnosis of RPF was made by a PET scan. A true-cut biopsy of the vast fibrotic retroperitoneal plaque around the abdominal aorta identified a diffuse invasive carcinoma with the origin of receptor-negative breast carcinoma. She started with palliative chemotherapy. In conclusion, RPF with a typical location for idiopathic RPF mimicked recurrence of cancer.

Discussion: Idiopathic RPF is a rare disease which may result in obstructive uropathy and renal failure. Secondary RPF should be excluded by histological examination in patients with a history of invasive lobular carcinoma.
Mornings are the worst: adverse event of pembrolizumab

D. de Groot, P. van den Berg
Tergooi Ziekenhuis, Afdeling Interne Geneeskunde, Hilversum

A 82-year-old male was treated for a metastatic urothelial carcinoma with pembrolizumab, a humanized anti-programmed cell death 1 antibody. On routine follow-up visit, the patient mentioned complaints of headache, proximal muscle and joint pain in both shoulders and hips. It started after the eleventh cycle of pembrolizumab. The pain was more prominent in the morning, upon getting up from bed and improved as the day progressed. After a period of rest during the day his complaints worsened. Patient denied any prior history of similar symptoms. Examination was unremarkable. Especially no fever or signs of arthritis. Differential diagnosis included immune related adverse events like myositis or polymyalgia rheumatica or progression of his malignancy with bone-metastases. Initial work-up revealed an erythrocyte sedimentation rate of 63 mm/h and a C-reactive protein of 21 mg/dL. Laboratory test showed no clues for myositis, a more common adverse event of immune checkpoint inhibitors, since creatinine kinase of 61 U/L was low. A PET-scan revealed FDG uptake in the soft tissues of both shoulder and hip joints and in the interspinous bursa of the cervical and lumbar spine. The vasculature showed no FDG uptake. Which concludes the patient has developed polymyalgia rheumatica probably caused by an immune-related adverse events of pembrolizumab. Although a paraneoplastic syndrome can't be excluded. Pembrolizumab therapy was interrupted and low-dose prednisone was administered.

This case raises awareness for rheumatic and myoskeletal autoimmune adverse events during immune checkpoint inhibitor therapy even after a long time of treatment. Literature shows these events are not dose-dependent.
Topiramate intoxications - Literature review and the first case report of a massive suicidal intoxication with toxicokinetic data following hemodialysis

T. Schutte, A. van Tellingen, J. van den Broek, M. ten Brink, M.G. van Agtmael-Boerrigter
Zaans Medisch Centrum, Afdeling Interne geneeskunde, Zaandam

**Background:** Topiramate is increasingly used, and has multiple (new) indications as anti-epileptic, anti-migraine, mood stabilizing and anti-depressant drug. Unfortunately, topiramate itself is associated with suicidal ideation and attempted suicides. Serious topiramate intoxications have been described, however indications and effect of interventions in severe intoxications including hemodialysis seem expert-based and lack empirical evidence. We aim to review the literature on topiramate intoxication cases and describe the first topiramate intoxication with toxicokinetic data following hemodialysis.

**Case:** A 41 year old women who intentionally ingested ~25500 mg topiramate was admitted to our emergency room. She was hypotensive and comatose followed by seizures, refractory to conservative management. Within three hours we initiated hemodialysis and measured topiramate concentrations before (313.5 mg/l) and after 3 hours of hemodialysis (132.5 mg/L), with resolution of symptoms.

**Methods:** Literature review using the PubMed database. Included articles were reviewed for symptoms, management (including acute hemodialysis), toxicokinetic data and outcomes.

**Results:** We found 53 hits in the PUBmed database, 21 were eligible for data extraction. These articles reported 22 individual cases. The majority of patients were female (n = 16, 80%) and their age ranged 2-44 years (median 21). The ingested topiramate concentration was reported in 13 cases, ranging 4.0-218.2 mg/kg. Topiramate concentrations were reported in 5 cases, ranging 3.7-356.6 mg/L (reference therapeutic range 2-30 mg/L). In none of the cases hemodialysis was used.

**Conclusion:** Serious topiramate intoxications can result in seizures and hemodynamic instability. Hemodialysis is used infrequently. If symptoms are refractory to symptomatic treatment, this case demonstrated hemodialysis reduced topiramate concentrations (~50%) and symptomatology.
Physician Suicide: A Scoping Review

T.I. Leung1, S. Pendharkar2, C.Y.A. Chen1

1Universiteit Maastricht; Academisch ziekenhuis Maastricht/MUMC+, Faculty of Health, Medicine and Life Sciences, Maastricht, 2Division of Hospital Medicine, The Brooklyn Hospital Center, New York, NY, USA

Background: Suicide is a stigmatized phenomenon that affects physicians at a higher rate than the general population. Physicians and trainees tragically continue to die by suicide or experience suicide attempts, thoughts or ideation. This suggests that knowledge and implementation gaps towards prevention persist. The aim of this scoping review was to map the landscape of published research and perspectives on physician suicide. This could enable community learning towards preventing physician suicidal behaviors.

Methods: We searched Ovid MEDLINE, PsycInfo, and Scopus for English-language journal publications from August 21, 2017 through April 28, 2018. Inclusion criteria were a primary outcome or thesis focused on suicide (including suicide death, attempts, and thoughts or ideation) among medical students, residents, or attending physicians. Opinion articles were included. Exclusion criteria were studies of only physician burnout, mental health or substance use disorders. This yielded 1,596 references; 348 references passed to full-text review. Data extraction was performed and articles were annotated with key concepts. Annotations were condensed into a core set of themes and visualized in a thematic map, or network graph.

Results: The earliest article is 1903 editorial; 210 (60.3%) articles were published from 2000 to present; 142 (40.8%) were opinion articles. Of the remaining 206, 84 were cross-sectional studies. Thirteen articles described interventions. Authors from 37 countries published about physician suicide.

Conclusions: Physician suicide is a global phenomenon. Most articles focused on mental health and other risk factors, and most were published in the past two decades. Few interventions exist to prevent physician suicides.
A 31-year-old woman came to the emergency department because of dyspnoea and right-sided chest pain related to the menstrual cycle. The patient had right sided pleural effusion and anemia. Thoracentesis revealed a hematothorax. It was decided not to do a thoracoscopy due to a hemodynamic stable situation. The patient received subsequently hormonal menstrual suppression treatment. In follow up she slowly recovered.

Discussion: Thoracic endometriosis (TE) in premenopausal women is one of the causes of secondary pneumothorax and/or (less common) hematothorax in women. According to the literature, 1 in 3 premenopausal women with pneumothorax can be diagnosed with ‘catamenial pneumothorax’. Hematothorax in thoracic endometriosis is less common. The diagnosis is often not made in practice, even though treatment is significantly different than that of primary pneumothorax and/or hematothorax. Infertility, earlier proven abdominal endometriosis and chest pain linked to menstruation are indications of thoracic endometriosis.
Systemic sclerosis (SSc) is a heterogeneous systemic autoimmune disease characterized by inflammation, micro-angiopathy and fibrosis, affecting skin and internal organs. Internal organ involvement, including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), has an unfavourable impact on survival, also in early disease. Identifying patients at risk of developing early organ involvement would be useful to optimize screening and treatment. The objective was to create prediction models for the 5-year development ILD, PAH and death.

A European multicentre inception cohort was created. For modelling, predefined clinical variables with known predictive value were used. Univariate and multivariate regression analysis were done to select baseline predictors and build the models. The models were tested using the area under the receiver operating characteristic (ROC) curve comparing observed and expected frequencies.

From 735 patients: 23% developed ILD; 8% developed PAH; 12% died. The ILD-model included diffuse cutaneous SSc (dcSSc) (Odds ratio (OR) 1.8), SSc-disease-duration< 3 years=““ or““ 4=““ puffy=““ fingers=““ or““ 1=““ 6=““ and=““ anti-topoisomerase-i-antibodies=““ or““ 1=““ 8=““ the=““ pah=““ model=““ included=““ age=““> 65 years (OR 3.2), FVC < 70% (OR 2.5) and DLCO < 55% (OR 1.9). Death was predicted best by age>65 years (OR 4.1), male gender (OR 1.9), no anti-centromere-antibodies (OR 0.5), proteinuria (OR 1.9), FVC < 70% (OR 1.8), PAH at diagnosis (OR 10.1). The AUC of the three models was 0.66; 0.66 and 0.70, respectively.

We have shown the possibility to predict ILD, PAH and death using variables available at the moment of SSc-diagnosis. Discriminatory performance of the models was suboptimal, further research is necessary to improve performance.
Prevalence and management of cardiovascular risk factors in ANCA-associated vasculitis: a cross-sectional study in the Netherlands and Canada

E. Houben¹, A. Mendel¹, J.W. Van der Heijden¹, S. Simsek¹, W.A. Bax¹, S. Carette², A.E. Voskuyl³, C. Pagnoux⁴, E.L. Penne⁵
¹Noordwest Ziekenhuisgroep, Afdeling Interne Geneeskunde, Alkmaar; ²Mount Sinai Hospital, Department of Rheumatology, Toronto, Canada; ³Amsterdam UMC, Afdeling Nefrologie, Amsterdam

Background: Patients with ANCA-associated vasculitis (AAV) are at increased risk of cardiovascular (CV) disease. The aim of the present study was to determine the prevalence of CV risk factors in patients with AAV and to evaluate the management of CV risk factors according to current guidelines.

Methods: A cross-sectional study was performed in patients with AAV in the Netherlands and Canada. Information on traditional CV risk factors, as well as markers of inflammation and kidney function, were collected. Their prevalence and treatment were studied and compared with recommendations in current guidelines.

Results: A total of 144 consecutive patients with AAV were included (71 from the Netherlands; 73 from Canada). Mean age was 62 ± 15 years, and 56% were male. The mean disease duration was 7.0 ± 6.6 years; 69% had granulomatosis with polyangiitis, 17% microscopic polyangiitis and 14% eosinophilic granulomatosis with polyangiitis. Mean body mass index was 28 ± 6 kg/m² and 65 patients (45%) had an estimated glomerular filtration rate < 60 ml. The mean C-reactive protein was 6.5 ± 12.3 mg/l. Dyslipidemia was present in 69% and hypertension in 72%. In 36% and 25% of the included patients, blood pressure and dyslipidemia, respectively, were not managed in accordance with national guidelines.

Conclusion: Patients with AAV have a high prevalence of traditional CV risk factors. Whether past or persistent inflammation and chronic kidney disease further increases the CV risk remains to be studied. Strict adherence to CV risk management guidelines should be encouraged.
A 60-year-old patient presented to the emergency department with blurred vision. Her medical history included arthralgia for which she was analyzed by an internist four months prior without an explanatory diagnosis. Laboratory findings at that time were, besides a positive ANF, normal. At presentation, physical examination showed a high blood pressure of 240/120 mmHg, facial telangiectasia, and minimal sclerodactyly. Fundoscopy showed hypertensive retinopathy grade 4. Blood results showed an acute kidney injury (eGFR 9 ml/min/1.73 m²), anemia, and thrombocytopenia. Patient was admitted to the ICU for treatment with intravenous labetalol. The kidney function did not recover, and patient started dialysis. The findings at physical examination raised the suspicion of systemic sclerosis. A renal biopsy was performed and showed onion skin lesions with glomerular ischemic changes compatible with scleroderma renal crisis (SRC). Anti RNA polymerase III antibody was positive, which is a serologic predictor for renal involvement in systemic sclerosis. We started treatment with an ACE-inhibitor and patient was referred to the rheumatologist.

**Discussion:** SRC is a rare but severe complication of systemic sclerosis. It is typically characterized by malignant hypertension and acute renal failure. Presenting symptoms include headache and blurred vision. Be aware of subtle signs like small facial telangiectasia and not well understood arthralgia, since that can form important clues to the diagnosis. The blood pressure should be aggressively controlled. The prognosis has been substantially improved since the advent of ACE-inhibitors. It can lead however to end stage kidney disease with need for long-term dialysis or a kidney transplantation.
It’s never PAN... or is it?

M. Kameh Khosh, R.J. Goekoop, D. Soonawala
Haga ziekenhuis, Afdeling Interne geneeskunde, Den Haag

Case: A 72-year-old woman presented with fever and arthritis of the right elbow. Five years before, she had been diagnosed with polyarteritis nodosa (PAN) following an extensive work-up for fever, malaise, weight loss, high ESR and CRP, and large ulcerative skin lesions with dermal vasculitis. Over the course of her disease, she had a relapse with cardiac involvement and had been treated with prednisone and cyclophosphamide. PAN had recently relapsed again later, with constitutional symptoms and mononeuritis multiplex of the ulnar nerve, for which she was being treated with prednisone, azathioprine and rituximab. Fluid aspirated from the elbow showed *Mycobacterium kansasii*. She was treated with rifampicin, ethambutol and isoniazid. Two weeks later she was re-admitted with asthenia, fever, headache, vomiting, anemia (Hb 5.1 mmol/L), thrombocytopenia (93x10⁹/L), high LDH (1395 U/L) and oliguric kidney failure. After analysis of her blood, a tentative diagnosis of thrombotic micro-angiopathy of unknown cause was made. She was treated with prednisone, plasmapheresis and dialysis. Her condition deteriorated and one week after she had been admitted, she died from respiratory failure due to pulmonary edema. The result of a plasma sample for CMV came back positive (PCR log 4). To our surprise, the autopsy showed typical signs of extensive PAN in the heart and kidneys, with transmural obliterative necrotizing inflammation of medium-sized arteries and thrombosis and infarction in down-stream arterioles and tissue. Conclusion: This case illustrates that CMV reactivation may potentially exacerbate PAN, leading to a fulminant course with fatal outcome.
Do we reach LDL-c treatment targets in patients with heterozygous Familial Hypercholesterolemia in the Netherlands?

K.E. Siegers¹, S. Hamkour¹, F.J. Visseren¹, M.A. van de Ree³, L. Louter¹, R.E. Roeters van Lennep¹, B.P.M. Imholz⁴, C. Koopal²

¹University Medical Center Utrecht, Department of vascular medicine, Utrecht, ²Diakonessenhuis, Department of vascular medicine, Utrecht, ³Erasmus Medical Center, Department of vascular medicine, Rotterdam, ⁴Elisabeth-Tweesteden Hospital, Department of vascular medicine, Waalwijk

Background: Heterozygous familial hypercholesterolemia (heFH) affects 1 in 240 people in the Netherlands. HeFH is an autosomal dominant hereditary disorder that results in elevated plasma LDL-cholesterol (LDL-c) levels and 10-fold increase in cardiovascular disease (CVD) risk. HeFH patients are treated with lipid-lowering therapy to attain the recommended LDL-c target of ≤ 2.5 mmol/l for patients without CVD and < 1.8 mmol/L for patients with CVD. In this study we evaluated treatment and treatment target attainment in patients with heFH.

Methods: A cross-sectional study was performed in 2 academic hospitals and 2 non-academic teaching hospitals in the Netherlands. Information on clinical characteristics, use of lipid-lowering therapy, reasons for not attaining treatment goals and plasma lipids was obtained from patient records. Determinants for treatment target attainment were analyzed using logistic regression.

Results: A total of 1723 patients with heFH were included. Of these, 15% had a history of CVD. 94% of patients used a statin and 21% of the patients with CVD used a PCSK9 monoclonal antibody. In patients without CVD 31% had an LDL-c ≤ 2.5 mmol/l, and 20% of CVD patients had an LDL-c < 1.8 mmol/L. Age, presence of CVD and hypertension increased the probability of LDL-c treatment target attainment. Most common reasons for non-attainment of target were the use of maximal lipid-lowering treatment, side effects and physician satisfaction.

Conclusion: Patients with heFH often do not attain the recommended LDL-c treatment target, leaving patients at high residual cardiovascular risk and emphasizing the need for optimization of lipid-lowering treatment in this high-risk patient population.
Dalteparin and anti-Xa: a complex interplay of therapeutic drug monitoring

E.D.P. van Bergen¹, A. Huisman², P.M.J. Welsing², M.A. de Winter², M.B. Rookmaaker², H.A.H. Kaasjager², M. Nijkeuter²
¹St. Antonius Ziekenhuis, Afdeling Interne Geneeskunde /MDL, Nieuwegein, ²UMC, LKCH, Utrecht

Background: Monitoring of low-molecular-weight heparins is generally not required. However, guidelines advise to monitor anti-Xa levels in patients with renal insufficiency, in patients with a BMI above 50 and in pregnancy. Measuring anti-Xa levels is a complex clinical challenge since sampling should be performed three to five hours after subcutaneous injection and after steady state concentrations have been reached. Strict compliance is pivotal for justified dose adjustments and we questioned the compliance to our protocol.

Methods: We included patients ≥18 years receiving therapeutic dalteparin in the UMCU, a Dutch academic medical center. Patients with a first anti-Xa level measured between 23 February 2017 and 30 December 2017 were selected. According to our local guideline, monitoring anti-Xa activity is indicated in patients on therapeutic doses of dalteparin who are pregnant, morbidly obese (BMI > 50) or have renal insufficiency (clearance < 60 ml/min). Accurate sampling was defined as measuring levels after at least 3 injections and 4 hours after injection. The indication for and frequency of compliance to our protocol describing therapeutic monitoring of anti-Xa was assessed.

Results: 158 patients with 396 anti-Xa levels were included. 41% (65/158) of all first anti-Xa levels were drawn without appropriate indication. 48% (211/396) was sampled incorrect and 25% (53/211) was followed by a dose adjustment. In total, 74% (293/396) was not indicated or performed at the wrong time.

Conclusion: Monitoring anti-Xa levels is a complex clinical challenge. This study showed that non-compliance with recommendations for anti-Xa monitoring was high, often resulting in unjustified dose adjustments.
Extended anticoagulation for unprovoked venous thromboembolism: a survey on physicians’ considerations and guideline adherence

M.A. de Winter, G.C.P. Remme, H.A.H. Kaasjager, M. Nijkeuter
UMC Utrecht, Afdeling Interne Geneeskunde, Utrecht

Background: In patients with unprovoked venous thromboembolism (VTE), treatment duration should be decided by weighing risk of bleeding versus risk of recurrent VTE, considering patient’s preference. Because both risks differ between individuals, this ambiguous recommendation presumably leads to wide variation in clinical practice. We sought to identify physician’s considerations when deciding between short-term and extended anticoagulation and to assess how current guidelines are put to practice.

Methods: An online, 33-item survey was developed, containing questions on clinical practice, considerations regarding treatment duration, use of and need for risk scores and information tools and shared decision-making. The survey was distributed to internists, pulmonologists and residents treating patients with VTE in the Netherlands.

Results: Respondents were 69 internists and 73 pulmonologists, including 24 residents. Extended treatment is preferred by 73% (104/142) of physicians. Most important determinants for extended treatment were, in ranking order: patient’s preference, active malignancy, low estimated bleeding risk, history of VTE and hemodynamic instability during previous VTE. Most important determinants for short-term treatment were history of frequent falls, history of major bleeding, previous bleeding during anticoagulation, patient’s preference and thrombocytopenia. Although existing risk scores are infrequently used, physicians express their need for scores combining risks of recurrence and bleeding for individualized decision-making.

Conclusion: Whereas most participants follow the recommendation to prescribe indefinite treatment in absence of contraindications, mentioned rationale is not always supported by evidence. Future research should clarify the prognostic value of unsupported determinants. Moreover, a clinically useful decision tool combining recurrence risk and bleeding risk is warranted.
Determination of the value of color Doppler ultrasound in patients with a clinical suspicion of giant cell arteritis

B.I. Kaandorp1, F. Stam1, H.G. Raterman1, M. Gamala1, L.B. Meijer-Jorna2, F.B. Kalb1, J.W. Wallis1
1Noordwest Ziekenhuisgroep, Department of Radiology, Alkmaar, 2Symbiant Pathology Expert Centre, Symbiant Pathology Expert Centre, Alkmaar

Background: Prompt diagnosis of giant cell arteritis (GCA) is necessary to prevent visual loss. Color Doppler ultrasound (CDU) has been proposed as a fast available and non-invasive diagnostic tool. The purpose of this study is to determine the diagnostic value of CDU for GCA.

Methods: 99 patients with a clinical suspicion of GCA with a maximum of 1 day corticosteroids were included. CDU from both temporal arteries and frontal and parietal branches was performed. CDU is considered as positive in the presence of a halo ≥ 0.6 mm, a stenosis or occlusion. The diagnosis one year after inclusion is used as reference test, determined by one internist and one rheumatologist, blinded for the CDU results. We also used the classification criteria for GCA developed by the American College of Rheumatology (ACR).

Results: In 26 patients the diagnosis after one year was GCA. Of these, 58% showed abnormal findings in CDU, 81% were positive to the ACR-criteria. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CDU for the diagnosis GCA were 58%, 93%, 75% and 86% respectively. The ACR criteria had a sensitivity, specificity, PPV and NPV of 81%, 58%, 40% and 89%, respectively. For the diagnosis cranial-GCA (C-GCA, 20 patients) CDU sensitivity, specificity, PPV and NPV were 75%, 91%, 68% and 94%, respectively. Sensitivity, specificity, PPV and NPV of the ACR-criteria for C-GCA were 85%, 57%, 33% and 94%, respectively.

Conclusion: CDU appears to have good diagnostic value compared to the ACR-criteria for GCA, particularly for C-GCA.
Thrombin generation is associated with bleeding risk in patients on dual antiplatelet therapy

C.P.D.M. de Breet1,2, S. Zwaveling3, R.H. Olie3, D. Huskens1, J. Konings1, M.J.A. Vries2,4, R.C.G.M. van Oerle2, Y.M.C. Henskens2, H. ten Cate2
1Maastricht Universitair Medisch Centrum+, Department of Internal Medicine, Maastricht, 2Maastricht University, Department of Biochemistry - CARIM, Maastricht, 3Synapse Research Institute, Maastricht, 4Jeroen Bosch Ziekenhuis, Department of Internal Medicine, ’s-Hertogenbosch

Background: Patients using Dual Antiplatelet Therapy (DAPT) after Percutaneous Coronary Intervention (PCI) are at risk for bleeding. Traditional coagulation tests (activated partial thromboplastin time and prothrombin time) and platelet function tests correlate poorly with clinical bleeding in these patients. Previous research has reported that thrombin generation (TG) could detect a bleeding risk in patients with severe congenital coagulation factor deficiencies and anticoagulant therapy, but cannot detect diminished platelet activity by DAPT in platelet poor plasma (PPP). We aim to investigate whether TG in PPP might predict a bleeding tendency in patients using DAPT.

Methods: 1 and 6 months after PCI TG was measured in PPP of high-risk patients on DAPT. During a 12-month follow-up, clinically relevant bleedings during DAPT of 93 patients were reported. TG was compared between patients with and without bleeding.

Results: 1 month after PCI, patients with bleeding (n = 8) showed a significantly lower Endogenous Thrombin Potential (ETP) (837.26 nM*min ± 11.23 vs. 1136.16 nM*min ± 229.59; p < 0.001) and Peak (93.58 nM ± 17.02 vs. 138.56 nM ± 42.03; p = 0.004) in PPP compared with patients without bleeding (n = 85). This effect remained visible 6 months after PCI between patients with (n = 4) and without bleeding (n = 64) (ETP 844.05 nM*min ± 211.69 vs. 1045.86 nM*min ± 190.07; p = 0.044, Peak 92.13 nM ± 26.41 vs. 129.76 nM ± 35.35; p = 0.041).

Conclusion: High-risk patients on DAPT with clinically relevant bleeding during follow-up have a significantly lower ETP and peak in PPP. This means TG might have potential to identify patients with a high bleeding risk. For those patients, DAPT could function as a ‘second hit’.
The inflammatory and atherosclerotic profile of patients with primary hyperaldosteronism

C.D.C.C. van der Heijden1, E.M.M. Smeets1, E.H.J.G. Aarntzen1, M.P. Noz1, H. Monajemi2, J. Deinum1, L.A.B. Joosten1, M.G. Netea1, N.P. Riksen1

1Radboudumc, Afdeling Interne Geneeskunde, Nijmegen, 2Rijnstate Ziekenhuis, Afdeling Interne Geneeskunde, Arnhem

Background: Primary hyperaldosteronism (PA) is associated with a strongly increased cardiovascular event rate, but the underlying mechanism is incompletely understood. An important hypothesis is that aldosterone accelerates atherosclerosis by activating innate immune cells, as shown in animal models. Since human data are currently lacking, we aimed to extensively study the multifaceted inflammatory and atherosclerotic profile of PA patients.

Methods: In 15 untreated patients with PA and 15 controls with essential hypertension (ET) we investigated peripheral blood leukocyte composition, monocyte subpopulations, several circulating inflammatory markers and ex vivo cytokine production. Macrophages, cultured by differentiating isolated monocytes in patient-own serum, were stored for RNA analysis. Vascular wall inflammation was investigated with FDG-PET.

Results: Aldosterone levels positively correlated with neutrophil counts, the neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratio, and negatively correlated with lymphocyte counts. Circulating inflammatory markers and ex vivo cytokine production did not differ between patients and controls. Macrophages of PA patient were characterized by an increased mRNA expression of pro-inflammatory TNFA. Data on vascular wall inflammation assessed with FDG-PET will be available at the time of the Nederlandse Internistendagen 2019.

Conclusion: Although circulating inflammatory parameters and ex vivo cytokine production capacity are similar in patients with PA compared to control patients with ET, our data suggest pro-inflammatory changes to the peripheral blood cell composition, as well as pro-inflammatory macrophage properties in PA. PET scan imaging of the vascular wall will conclusively answer the question if PA has to be considered a chronic inflammatory disorder accompanied by accelerated atherosclerosis.

[MK1] Link invoegen naar de pagina waar de sectie Oral Presentations begint; idem voor alle volgende sectiekoppen.

[MK2] Link invoegen naar de pagina waar deze oral presentation begint. En dat voor elk volgend abstract in deze uitgave.