Netherlands
The Journal of Medicine

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Biosis database; embase/excerpta medica; index medicus (medline) science citation index, science citation index expanded, isi alerting services, medical documentation services, current contents/clinical medicine, PubMed.

ISSN: 0300-2977

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The annual subscription fee within Europe is € 798, for the USA € 836 and for the rest of the world € 957. Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis.

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EDITORIAL

Towards a hospital-wide integrated system for quality and safety of health care

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Quality of health care has obviously always been a concern of health care professionals. However, while in the past this was mostly viewed as the discretionary responsibility of the individual doctor or nurse, over the last decades a more integrated view on health care quality has been developed and implemented in most health care institutions. Modern medicine has rapidly evolved into a highly complex system in which various professionals take part and have to collaborate to achieve an optimal outcome.[1] Hence, just being a very good doctor or nurse is not good enough anymore and attention should be given to the entire process of health care delivery surrounding the patient.[2] In the discussion on quality of health care, patient safety has received special attention. To put it simply, patient safety means that a patient in the process of his or her treatment and care will not be damaged by the treatment itself or the circumstances adjoining this treatment or associated care. Moreover, to prevent this damage, specific measures should be installed to guarantee that patients are not exposed to potentially harmful situations.

Integrated safety systems in health care settings are generally based on three pillars: (1) (standardised) organisation of health care processes; (2) education and training of health care workers; and (3) reporting and analysis of (near) mistakes, incidents, or complications.

Organisation of health care processes encompasses an institution-wide implementation of a standardised set of rules and agreements according to which health care is delivered. Obviously, many procedures in our hospitals have implicitly been established but a critical appraisal of processes in health care shows a clear lack of standardised delivery of care in many places. Do you know precisely how your colleague handles a patient with abdominal complaints in his outpatient clinic or exactly how your resident manages a patient with sudden dyspnoea at night? Are you sure that you all check for potential allergies in each patient before prescribing antibiotics and are you certain that, without exception, all bedridden patients receive adequate thrombosis prophylaxis in your ward? For surgical and other invasive procedures check lists have been developed and evaluated and strict implementation has been shown to reduce harmful complications and even mortality to a significant extent.[3]

Another focus area in improving health care outcome is the critically ill patient. Early recognition and aggressive treatment of patients with compromised vital functions has proven to be crucial for better outcome of care.[4] For patients in general wards, often with less sophisticated continuous monitoring of vital functions, Early Warning Scores have been developed, which can trigger attention to patients at risk and guide physicians and nurses in the management of these patients, for example by deciding to transfer them to a facility with closer monitoring and more intensive care.[5-7] In this issue of the *Netherlands Journal of Medicine,* Van Rooijen *et al.* report on the optimal threshold of such an Early Warning Score in a general medical and surgical department of a large teaching hospital.[8] On the basis of more than 70,000 scores, they were able to define which scoring threshold had the optimal sensitivity and specificity for the Early Warning Score for necessary interventions. It is clear that systems such as checklists and Early Warning Scores could be helpful tools in avoiding harmful complications to patients in our hospitals.

Education and training of doctors, residents, nurses and other health care workers is another issue that may contribute to quality of care and patient safety. Continuous attention to proper education and rigid documentation of who is competent (or not) to perform procedures, to work with certain equipment, to prescribe and administer potentially dangerous drugs, and to deliver specific care is required to guarantee that hospital workers are up-to-date with the problem they are faced with and tools they have

to work with. Too often knowledge and skills are taken for granted, whereas it is clear that many gaps may exist in actual competency.[9]

Lastly, and importantly, reporting of incidents and analysis of their causes is of paramount importance. Often, meticulous examination of a complication or incident is very helpful to avoid similar situations in the future.[10,11] A prerequisite of adequate reporting and analysing unwanted situations is the willingness of staff to report (near) incidents and mistakes and an environment in which blameless discussion of errors has been created.[12]

The setting in which complications are registered may also be of importance. At present, most institutions focus on incidents occurring during hospitalisation; however, many complications may occur after discharge or in the outpatient setting. In this issue of the *Netherlands Journal of Medicine,* Magdelijns *et al.* report on their investigation whether the emergency department may be the right place to get a better inventory of these incidents.[13] They demonstrate that a considerable number of complications were indeed detected by this registration. Of note, most complications were related to medication (in particular anticoagulants), which is similar to previous studies,[14] but also complications related to chemotherapy or interventions were markedly prevalent. Remarkably, the authors estimated that up to 28% of complications were potentially preventable.

Taken together, our patients and we as health care workers have much to gain from improved quality and safety measures in our institutions and integrated institution-wide systems related to quality and safety seem to be of great importance to achieve our goal of better health care outcomes.

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REVIEW

Bariatric surgery is an effective treatment for morbid obesity

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ABSTRACT

The global obesity epidemic is also affecting the Netherlands, paralleled by a proportional increase in the number of morbidly obese persons. Bariatric surgery has been included as a treatment for morbid obesity in the Dutch Guideline for Obesity (2008). Nonetheless, bariatric surgery is applied in only a limited number of morbidly obese subjects in the Netherlands. Based on the most recent literature and Dutch statistics, this review provides a summary of current knowledge on the impact of obesity on health and health care and highlights the effective role of bariatric surgery in reducing this threat to public health.

KEYWORDS

Bariatric surgery, morbid obesity, treatment

INTRODUCTION

The obesity epidemic is growing and a call for action was recently launched.[1-4] Overweight/obesity means disproportionally more weight in relation to body height and is quantified by the body mass index (BMI; weight in kilograms divided by length in squared meters, kg/m^2). A BMI >25 kg/m^2 represents overweight, >30 kg/m^2 obesity, and >40 kg/m^2 morbid obesity.[5] The prevalence of obesity is expected to increase further.[6]

Standard primary treatment of obesity consists of diet and lifestyle interventions.[7] Medical therapies are not widely used due to their modest effect.[8] A relatively novel treatment option is bariatric surgery, which consists of several surgical procedures aimed at losing weight. Bariatric surgery is currently the only effective treatment for morbid obesity and leads to relevant sustained weight loss as well as a decrease in the prevalence and incidence of comorbidity.[9-11] Nonetheless, bariatric surgery is only available for a limited proportion of patients with morbid obesity. Although the number of subjects who were eligible for bariatric surgery in the Netherlands was 220,000 in 2007,[12] only 3500 patients underwent surgery in 2008.[13] Moreover, within the public debate, the notion often prevails that the complications resulting from surgical intervention outweigh the positive results of bariatric surgery.[14,15]

Obesity benefits from a multidisciplinary approach, which should include bariatric surgery.[16,17] The aim of this article is to review the possibilities of surgical treatment of morbid obesity. For specific patients the health benefit is clear and it is of importance that these patients are being informed of this effective and safe treatment of their obesity.

PREVALENCE, INCIDENCE, AND TRENDS OF OBESITY

Dutch data from the Central Organisation of Statistics (Centraal Bureau voor de Statistiek; CBS) show a twofold increase in the number of adults with obesity (BMI > 30 kg/m^2) during the past 20 years.[18] In the period 1981-2009 the number of obese men increased from 4.0% to 11.2%, and the number of obese women increased from 6.2%

to 12.4%. It is unknown how many adults are morbidly obese, but in a report in 2003 from the Health Council (Gezondheidsraad) the number of morbidly obese adults was estimated at 1-1.5% after extrapolation of US and UK statistics.[19] In comparison, in 2007 in the US, 4% of men and 6% of women had a BMI >40 kg/m^2 which, according to forecasts, will increase to 5% and 10%, respectively, in 2030.[20] The UK population shows a similar trend with an increase from 1% to 3% in male adults, and from 3% to 6% in female adults.[20] Some other extrapolations show even worse scenarios.[21]

COMORBIDITY AND MORTALITY ASSOCIATED WITH OBESITY

The relative risk for coronary heart disease with a BMI of 26 kg/m^2 compared with a BMI of <21 kg/m^2 is 2 and 1.5 times higher in women and men, respectively.[22] The relative risk for diabetes mellitus type 2 (T2DM) is fourfold increased in men and eightfold in women and for hypertension about 2-3 fold in both men and women comparing a BMI of 26 kg/m^2 with <21 kg/m^2. These relative risks increase further when the BMI increases to >29 kg/m^2.[22]

Obesity and morbid obesity are associated with increased mortality amongst both men and women. A BMI of 30-35 kg/m^2 decreases median survival by 2-4 years, and a BMI of 40-45 kg/m^2 by 8-10 years.[23]

Furthermore, quality of life in patients with morbid obesity is decreased compared with patients with other chronic diseases. The occurrence of psychological problems such as depression, somatisation, inter-personal problems, low social adaptation, and low self-esteem seems to be higher in obese individuals.[24]

COSTS RELATED TO OBESITY

The overall costs related to morbid obesity consist of both costs for health care (direct) as well as absenteeism (indirect). Specific financial data related to morbid obesity in the Netherlands are not available, but, in general, health care expenses increase proportionally to the increase of bodyweight.[25] The most recent statistics from the Netherlands show significantly higher sick leave percentages (both related to frequency and duration of sick leaves) in employees with obesity (BMI >30 kg/m^2) compared with non-obese employees.[26]

In various countries obesity accounts for 2-6% of the total budget available for health care.[1] These costs are related to medical treatment of diseases such as T2DM and cardiovascular disease, and to the use of non-steroidal anti-inflammatory agents and other analgesics (relative risks vary from 4.1 to 9.2). These prescriptions result in a doubling of the total amount spent in obese versus normal weight subjects.[27] The association between BMI and coronary heart disease, hypertension, and diabetes largely explained these increased costs. The annual rates of inpatient days, number and costs of outpatient visits, costs of outpatient pharmacy and laboratory services, and total costs are related to obesity as well, with mean annual total costs being 25% higher among those with a BMI of 30 kg/m^2 to 34.9 kg/m^2 (rate ratio 1.25; 95% confidence interval 1.10-1.41), and 44% higher among those with a BMI of 35 kg/m^2 or greater (rate ratio 1.44; 95% confidence interval 1.22-1.71), compared with a BMI between 20 kg/m^2 and 24.9 kg/m^2.[25]

In the Netherlands, the yearly expenses related to obesity are estimated to be approximately 505 million Euros. This represents 1.6% of the total health care budget for adults of ≥20 years of age.[28] In 2002 the Public Health Council (Raad voor de Volksgezondheid en Zorg) estimated the indirect costs related to overweight and obesity as being 2 billion Euro per year. These costs will increase over time if the current trend in increasing prevalence in obesity mimics the situation in the US, resulting in a threefold increase per generation, consisting of 20 years each.[29] Already in 2000, the World Health Organization (WHO) declared that 'surgery is now considered to be the most effective way of reducing weight, and maintaining weight loss (BMI >35 kg/m^2 or above)', and that on the basis of cost/kg of weight lost, 'surgical treatment has been estimated, after four years, to be less expensive than any other treatment'.[30]

TREATMENT OF MORBID OBESITY

Dutch guideline on obesity[31]

Treatment of obesity aims at restoration of energy balance, i.e. a decrease in energy intake and an increase in energy expenditure. The Dutch guideline on obesity established in 2008 (Centraal Begeleidings Orgaan, CBO) recommends combined lifestyle interventions in order to lose weight and maintain weight loss eventually resulting in a clinical benefit on general health. The duration of this intervention should be at least one year. The composition of the energy-restricted diet should reflect a healthy balanced diet according to current guidelines on healthy food. Expertly guided and supervised physical activity programs are part of the intervention. Furthermore, cognitive behavioural therapy may be considered in addition to the treatment. Lastly, the role of medical treatment is limited. Only when conventional therapy fails, bariatric surgery may be considered in persons with a BMI >40 kg/m^2 or >35 kg/m^2 with comorbidity such as T2DM and/or hypertension (*table 1*).[32]

Table 1. *Criteria for bariatric surgery in the Netherlands*[31]

BMI > 40 kg/m² or >35 kg/m² with comorbidity such as T2DM and/or hypertension
Prior intensive treatment in a specialised obesity clinic/program
The patient is physically suitable for anaesthesia and surgery
The patient is willing to take vitamin preparations life long
The patient is willing to cooperate in long-term follow-up and understands the necessity for this

Effects on weight loss and comorbidity: conventional versus surgical treatment

A recent Cochrane review concluded that bariatric surgery results in more weight reduction than conventional treatment, and that the results will sustain for at least ten years.[33] The results of the landmark follow-up study conducted in Sweden, the Swedish Obese Subjects (SOS) study, documented lower morbidity and mortality rates as well as a sustained weight loss of on average 16% after ten years in favour of bariatric surgery. Furthermore, the prevalence of T2DM, dyslipidaemia, and hypertension was lower after two and ten years. Lastly, bariatric surgery is associated with a decreased number of people suffering from cardiovascular disease.[10,34] Two and six years after surgery, surgically treated patients needed less medication for cardiovascular disease or diabetes.[35]

In two recent studies, different types of bariatric surgery in severly obese patients with T2DM were compared with medical therapy. These two randomised controlled trials provide further evidence that surgery can be more effective than either standard or intensive medical treatment alone. After two years, rates of complete remission of diabetes were 75% for gastric bypass and 95% for biliopancreatic diversion (partial gastrectomy and gastroileostomy with a long segment of Roux limb and a short common channel), as compared with no remissions for medical therapy. In addition, dyslipidaemia improved significantly.[36] After one year, a glycated haemoglobin level of ≤6%, was achieved in 12% of patients in the medical therapy group versus 42% in the gastric bypass group and 37% in the sleeve gastrectomy group.[37] Finally, quality of life improved in subjects after bariatric surgery compared with a non-surgically treated group. Despite some weight regain after ten years, the score for quality of life remained higher in surgically treated patients.[38-40]

TYPES OF BARIATRIC SURGERY

At present, bariatric surgery is mainly performed laparoscopically, and consists of restrictive and/or malabsorptive components. The most frequently performed procedures are: 1) laparoscopic Roux-en-Y gastric bypass (LRYGB) which combines restrictive and malabsorptive components, 2) sleeve gastrectomy, which induces food restriction only and often serves as a bridge to a gastric bypass, and 3) adjustable gastric band (laparoscopic adjustable gastric band; LAGB) which is purely restrictive (*figures 1-3*).

Figure 1. *Gastric bypass*

Figure 2. *Gastric sleeve*

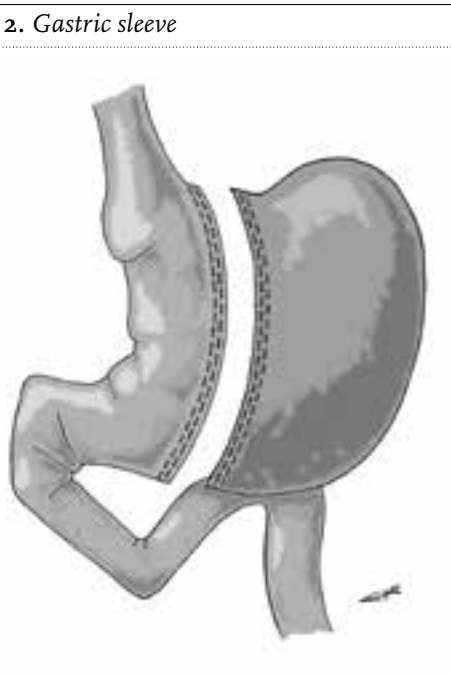

Figure 3. *Gastric banding*

The mechanisms explaining the sustained weight loss and metabolic improvement induced by RYGB have not been fully elucidated. The restrictive nature of this procedure only explains in part the lower caloric intake. The anatomical changes induced by bariatric surgery alter the secretion of classical hormones and gut peptides involved in food intake, satiety, reward and metabolic handling of nutrients.[41-44] Improvement of the features of the metabolic syndrome are mainly correlated to excess weight loss[45] but may be partly induced by these neuroendocrine changes occurring after bypass surgery. In addition, weight loss after surgery is associated with a lower inflammatory status that might contribute to the metabolic improvement after bypass surgery.[46]

The effectiveness of bariatric surgery is usually measured by means of the amount of weight loss. The most commonly used outcome parameter is the percentage loss of the overweight expressed as % excess weight loss. A meta-analysis, in which the two most commonly performed surgical procedures were compared (LAGB vs. LRYGB), showed that the median % excess weight loss 1 year after LRYGB was 26% higher than LAGB, with a more favourable effect on comorbidity.[47] After LAGB, weight regain might occur with the necessity to perform a second bariatric procedure.[48] Therefore, LAGB is currently not the preferred treatment option. The sleeve gastrectomy is relatively new as a primary bariatric intervention. Initially this type of surgery was performed specifically as an alternative to patients with extreme obesity (BMI >60 kg/m^2) or if LRYGB was not technically feasible. Short-term results are good,[49] but long-term results are still awaited.

COMPLICATIONS OF BARIATRIC SURGERY

In general, 30-day mortality after bariatric surgery is low, ranging from 0.09% to 0.3%.[50-52] The 30-day mortality of laparoscopically performed bariatric surgery is 0.07% versus 0.3% for open procedures.[51] The presence of cardiac, pulmonary, vascular, metabolic, and inflammatory comorbidity renders the patient more susceptible to complications such as fluid imbalances, complicated intubation, myocardial ischaemia, venous thrombosis, pulmonary embolism, and wound infection.[53,54] Anastomotic leakage is a severe complication and occurs in 0-5.4% of cases and strongly depends on the experience of the surgeon.[55,56] In general, the duration of hospital admission is usually short with a median duration of 1-2 days.[57] In order to prevent long-term complications of bariatric surgery, such as weight regain, nutritional and vitamin deficiencies, and glycaemic disorders, the Endocrine Society has provided a practical guideline with recommendations.[57]

VOLUME AND QUALITY OF BARIATRIC SURGERY

Approximately 40,000 bariatric procedures were performed in 1998 worldwide. This increased by 266% in 2003 and even increased further to 345,000 bariatric procedures in 2008. In the Netherlands an estimated 3500 patients were operated on in 2008.[13] However, in the Netherlands more people are eligible for bariatric surgery and it is estimated that the number of patients eligible for bariatric surgery will increase from 220,000 in 2007 to as many as 336,000 in 2012.[12] In the Netherlands, 16 hospitals perform bariatric surgery on a regular basis. The Dutch Society of Surgery (Nederlandse Vereniging voor Heelkunde; NVvH) has recently determined that bariatric surgery belongs to the category of 'both high-complex and low-complex, high-volume surgical interventions to which qualitative conditions for the health care institution apply'. To be eligible as a centre for bariatric surgery, a hospital has to fulfil 15 criteria (*table 2*). This quality standard demonstrates the specific and multidisciplinary nature of this type of care.[58]

Table 2. *Criteria for hospitals performing bariatric surgery in the Netherlands*[58]

1.	Presence of a department of Internal Medicine (Endocrinology) and Gastroenterology, with specific knowledge of morbid obesity and surgical treatment options
2.	Presence of a department of (interventional) Radiology
3.	Presence of an endoscopy unit
4.	Presence of specifically trained anaesthesiologists with experience in the treatment of bariatric surgical patients
5.	Presence of a multidisciplinary team (consisting of at least an internist/endocrinologist, dietician, psychologist, surgeon and nurse specialist) to take care of the intake procedure, needs assessment and counselling of patients
6.	Within the clinic all relevant disciplines must agree on the classification and treatment of different patient categories
7.	Presence of protocols for the surgical treatment of morbid obesity
8.	Presence of basic facilities, materials and tools used for morbid obese patients, such as waiting rooms, chairs, beds, scales, and recovery room and intensive care facilities
9.	Presence of an established contact with a reference centre for referral or consultation
10.	Acute surgery and surgical interventions for complications related to bariatric surgery are performed by surgeons from the clinic with sufficient experience in elective bariatric surgery, or arrangements with the centre for referral or consultation about these interventions must be defined
11.	The surgical department maintains a digital database in which treatment data and outcomes of treatment and complications of all patients are registered
12.	At least 100 primary bariatric procedures a year are performed
13.	It is recommended that departments that start with bariatric surgery shall initially be limited to simple procedures (laparoscopic gastric band placement) in low-risk patients. This includes patients with an ASA rating ≤ 3, no major abdominal surgery in the medical history, age < 60 years, and a BMI ≤ 45 kg/m² for men and ≤ 50 kg/m² for women
14.	It is recommended not to treat super obese patients (BMI > 50 kg/m²) nor to perform technically complex operations in the first 1 to 2 years until sufficient experience (at least 75-100 LAGB procedures) has been gained
15.	Complex bariatric procedures such as laparoscopic gastric bypass procedure, duodenal switch and sleeve resections are carried out only after sufficient experience with simpler procedures (minimum of 100 LAGB) and adequately trained professionals

CONCLUSION

Obesity is a major health problem with serious medical, psychological and socioeconomic consequences. Reduction of excessive body weight is associated with a decreased prevalence and incidence of obesity-related health problems such as diabetes, cardiovascular disease and psychological health. Bariatric surgery is a very effective treatment for morbid obesity with relatively limited complications, if performed by experienced surgeons. However, the number of potentially eligible patients with morbid obesity by far exceeds the current availability of bariatric surgery in the Netherlands.

Multidisciplinary teams, consisting of internists, gastroenterologists, surgeons, dieticians, nurse specialists and psychologists, should carefully select patients eligible for bariatric surgery and guarantee long-term structured follow-up. Studies that identify which subgroups of obese subjects will clinically benefit the most and which determinants predict clinically significant weight loss should be undertaken by performing multicentre studies nationwide. This will enable us in the future to perform these surgical procedures only in patients in whom a clear clinical benefit can be expected.

In the Netherlands bariatric surgery is performed in non-academic hospitals. Commitment of university hospitals to develop research programs in close collaboration with these bariatric centres is necessary to gain more insight into the long-term consequences of bariatric treatment. A national prospective registry and database of all patients who underwent bariatric surgery is another tool to monitor safety.

CONFLICT OF INTEREST

None to declare.

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Netherlands
The Journal of Medicine

REVIEW

Vascular manifestations of systemic lupus erythematosis

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune connective disease, where vascular lesions are one of the typical symptoms. The differentiation of the type of vascular complications in SLE is very difficult, sometimes impossible, and requires an in-depth immune and histopathological approach, and extensive clinical experience. It may play a key role in the choice of treatment strategy and prediction of patient prognosis. SLE is a prototype of a multisystem autoimmune connective tissue disease, marked by immune complex-mediated lesions of blood vessels in diverse organs. Therefore, awareness of the aetiology, pathophysiology, the clinical and histopathogical setting, and SLE-associated vascular complications is of great clinical significance. In this review, the spectrum of vascular abnormalities and the options currently available to treat the vascular manifestations of SLE are discussed.

KEYWORDS

Systemic lupus erythematosus, vasculitis, vasculopathy, antiphospholipid syndrome

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous manifestations, including internal organ damage, which can result in severe morbidity and even death and often requires aggressive immunosuppressive treatment. SLE is a connective tissue autoimmune disease, where vasculopathy is one of the most typical symptoms.[1] Vascular involvement is frequent in SLE patients and represents the most frequent cause of death in established disease. In this context, vasculopathy can be directly aetiologically implicated in the pathogenesis of the disease, presenting as an acute/subacute manifestation of lupus (e.g., antiphospholipid syndrome (APS), lupus vasculitis). Besides overt vessel obstruction, vascular disease in lupus, especially when affecting medium- and small-sized vessels, may contain both vasculopathic and vasculitic pathophysiological parameters.

Livedoid vasculopathy, a condition which can be observed in patients with SLE/APS or specific forms of systemic vasculitis (mainly polyarteritis nodosa and cryoglobulinaemia) is associated with chronic ulcerations of the lower extremities and characterised by uneven perfusion.[2] The pathogenesis of livedoid vasculopathy has not been fully elucidated, or rather, cannot be solely attributed to a particular mechanism, as both hypercoagulable states, as well as autoimmune diseases, appear to associate with and contribute to its development.[3]

The typical histological findings show dermal blood vessel occlusion.[4] The histopathological findings of intravascular fibrin, segmental hyalinisation, and endothelial proliferation clearly support the thrombotic parameter of its pathogenesis.[5] The presence of immunoreactants in the vessel wall and circulating immune complexes (such as rheumatoid factor) are in favour of its immunological component; the absence, however, of fibrinoid necrosis and inflammatory infiltration of the vessel wall differentiates livedoid vasculopathy from true vasculitides.

It is reported in 10-40% of patients, occurs more often in women (80%) than in men and may precede the development of a full-blown SLE.[6] Vascular lesions in SLE are commonly known as lupus vasculopathy; a typical lupus vasculitis with inflammatory and vascular wall necrosis and a thrombus in the lumen of the affected artery occurs less often.[7-9] However, the rate of thrombotic

events is higher in patients with disease of recent onset, when compared with patients with other autoimmune diseases and remains so throughout the course of the disease;[10] in the LUMINA study, which included multiethnic SLE patients of recent diagnosis, age, damage accrual at enrolment, and antiphospholipid antibodies as well as the use of higher dosages of glucocorticoids were associated with a shorter time interval to thrombotic events.[11] Appel *et al.*[8] provided an SLE vasculopathy classification including: non-complicated vascular deposits of immune complexes, non-inflammatory necrotic vasculopathy, thrombotic microangiopathy and true lupus vasculitis. Of all lupus vasculitis cases more than 60% involve leucocytoclastic inflammation, 30% are vasculitis with cryoglobulinaemia, and systemic vasculitis resembling polyarteritis nodosa constitutes about 6% of SLE vasculitides patients.[8,12-14] Other clinical syndromes of vasculopathy in patients from the discussed group include thrombocytopenia with thrombotic purpura, venous thrombosis, antiphospholipid syndrome and urticaria vasculitis, reported in 5% of SLE patients.[8] SLE-associated vasculitis may present different clinical courses. The broad spectrum of symptoms includes mild forms affecting only cutaneous vessels and also severe, catastrophic forms, with the development of organ complications, and vasculitis within the internal organs.[15,16] Lupus vasculitis is usually seen in cutaneous vessels, in renal glomeruli, coronary and brain vessels, the brain, lung alveoli and less often in the gastrointestinal tract.[1] In SLE, small-vessel vasculitis with necrosis of vascular walls has been found in lymph nodes.[17] Nevertheless, due to local deposition of immune complexes in the blood vessels, vasculitis may play an important role in the pathogenesis of necrosis in lupus lymphadenitis. These disorders closely mimic malignant lymphomas both clinically and pathologically; therefore it is necessary to do extensive clinical evaluation.[18]

It has to be stressed that cutaneous lupus vasculopathy is the most common manifestation of SLE, and is reported in 94% of patients with lupus vasculitis.[19,20] Mild forms are characterised by purpura, urticaria lesions or bullous lesions of extremities, and livedo reticularis on the trunk. It has been demonstrated that internal organ vessels are affected in 18% of SLE vasculitis patients. Renal vasculitis takes the shape of focal segmental glomerulitis with development of fibrinoid necrosis.[1] Lung vasculitis takes the form of necrotic alveolar capillaritis predisposing to pulmonary haemorrhage.[1] Brain vasculitis only occurs in about 10% of SLE patients and associated clinical symptoms are very variable: from mild cognitive dysfunction to severe psychosis and convulsions, local ischaemia and strokes.[1,21] The peripheral nervous system may also be affected by lupus vasculopathy leading to multifocal inflammatory mononeuropathies.[1] Mesothelium vasculitis may also occur and lead to gastrointestinal haemorrhage or perforation.[1]

ANTIPHOSPHOLIPID SYNDROME

The clinical APS, an autoimmune syndrome usually developing in the context of SLE, is a condition defined as a predisposition for arterial and/or venous thromboses and/or recurrent miscarriages or other obstetric emergencies (e.g., premature birth, preeclampsia) in association with haematological abnormalities and specific antibodies targeted against phospholipid-binding plasma proteins.[22] The most severe form of APS is catastrophic APS, which is characterised by widespread small-vessel thrombosis with multiorgan failure and more than 50% mortality.[23] It has been suggested that endothelial damage of whatever origin exposes endothelial cell phospholipids, which enables the adhesion of aPL antibodies.[19] In 1998, the preliminary classification criteria for APS were proposed at Sapporo, Japan.[24] Classification for this syndrome needed at least one clinical manifestation together with positive tests for circulating antiphospholipid (aPL) antibodies, including lupus anticoagulant or anticardiolipin, or both, at medium-high values, detected at least twice in six weeks. In 2006, classification criteria were updated (*table 1*).[25] Essentially, the clinical criteria remained unchanged,

Table 1. *Classification criteria for antiphospholipid syndrome*

Clinical criteria	
Vascular thrombosis	One or more clinical episodes of arterial, venous or small-vessel thrombosis in any tissue or organ, confirmed by objective criteria. Histopathology should show thrombosis without significant inflammation in the vessel wall
Pregnancy morbidity	One or more unexplained deaths of a morphologically normal foetus at or beyond 10 weeks' gestation OR One or more premature births of morphologically normal neonate at or before 34 weeks' gestation due to pre-eclampsia or placental insufficiency OR Three or more unexplained, consecutive, spontaneous abortions before 10 weeks gestation, excluding maternal anatomical or hormonal abnormalities, and excluding maternal and paternal chromosomal causes
Laboratory criteria	Medium/high titre IgG and/or IgM isotype anticardiolipin antibody in blood on 2 or more occasions at least 12 weeks apart using standard assays Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart Anti-β_2 glycoprotein-I IgG or IgM in blood on two or more occasions at least 12 weeks apart using standard assays.

however, two important modifications were made: the time elapsed between two positive determinations was extended to 12 weeks to assure the detection of persistent antibodies only; and anti-β2-glycoprotein I, both IgG and IgM, were added to the laboratory criteria. Notably, IgA isotypes, antiprothrombin antibodies, and antibodies directed against phosphatidylserine-prothrombin complex remained excluded from the criteria. During the last few years these modifications have been criticised, and the debate about the clinical implications of different antiphospholipid antibodies is still open.[26] Recent clinical studies have confirmed lupus anticoagulant as consistently the most powerful predictor of thrombosis.[27-29]

The pathogenetic action mechanisms of aPL antibodies are variable. When binding with membrane phospholipids aPL antibodies may inhibit reactions catalysed by them in the coagulation cascade, for example through inhibition of C and S protein activation.[30] These antibodies may also activate endothelial cell-mediated thrombin formation.[30] The binding of aPL antibodies with platelet membrane phospholipids binding protein predisposes to platelet activation and adhesion, with consequent thrombus formation. These antibodies probably also participate in complement system activation.[30] As a result, the aPL antibodies demonstrate proadhesive, proinflammatory and prothrombotic effects on endothelial cells.[30] Thrombosis within the context of APS may occur even in histologically normal vessels. However, in the majority of aPL-positive patients, seropositivity *per se* does not suffice for the development of clinical events. Thrombotic events seem to occur more readily in SLE patients with coexistent atherosclerosis.[31] Recently, the presence of microangiopathy, defined as capillary micro-haemorrhages, and diagnosed with the aid of capillaroscopy, has been proposed as an augmentary screening tool for aPL-seropositive patients who are prone to develop clinical thrombotic manifestations.[32]

Optimal treatment of APS patients is still controversial and is continually under review due to the small number of adequate clinical prospective studies. Treatment of APS patients must be based on the use of platelet antiaggregating agents or anticoagulants. In asymptomatic patients with elevated titres of aPL antibodies, additional vascular risk factors such as hypertension, hypercholesterolaemia, tobacco use or oral contraception containing oestrogen have to be addressed and treated.[33] In view of its low potential for toxic effects, many experts understandably recommend low-dose aspirin (combined with hydroxychloroquine) to be considered as primary thromboprophylaxis in SLE patients with lupus anticoagulant or persistently positive anticardiolipin, or both.[34]

APS patients who present with thrombosis have an elevated risk of suffering new thrombotic phenomena; the main treatment for that group of patients is antithrombotic treatment, rather than immunosuppression.[35] The present state of knowledge recommends treatment with oral anticoagulants for an indefinite amount of time and maintaining an international normalised ratio (INR) between 2 and 3 for APS patients with venous and arterial non-cerebral events.[36,37] Some studies have suggested that in APS patients with arterial thrombosis more aggressive treatment is needed with a target INR of more than 3 (INR 3-4).[38-40] Heparin and low-dose aspirin are the treatments of choice for APS in pregnancy. Neither conventional heparin nor low-molecular-weight heparin cross the placenta and, therefore, do not affect foetal development. Prolonged use of fractioned heparin has been associated with the development of maternal osteoporosis. Low-molecular-weight heparin is being used to treat these patients and seems to have the least effects on bone mass.[41] Heparin must be maintained throughout pregnancy and the postpartum period until the patient restarts oral anticoagulation. Thrombocytopenia associated with the presence of aPL antibodies is usually moderate and does not require treatment. Nevertheless, in the case of severe thrombocytopenia (less than $50 \times 10^9/\mu l$) treatment with corticosteroids, intravenous immunoglobulins or some immunosuppression drugs is usually effective.[42] B-cell depletion therapy with anti-CD20 (rituximab) monoclonal antibodies has been used recently in the treatment of severe thrombocytopenia.[43] The treatment of the catastrophic form of APS is the greatest challenge. Less severe cases can be managed with anticoagulation and high-dose steroids. However, in the case of life-threatening manifestations, either intravenous immunoglobulins or plasma exchange should be added.[44] There is not the same degree of agreement of intensity and duration of anticoagulation but we recommend it for the lifetime. Recommendations for APS treatment are summarised in *table 2*.

LUPUS VASCULITIS

Distinction of inflammatory lupus vasculitis from APS, which may present with similar clinical manifestations, is of major significance in terms of clinical management. Inflammatory vascular disease is triggered by the in situ formation, or the deposition, of immune complexes within the vessel wall.

Vasculitis is an inflammation of vessel walls.[45] This vascular inflammatory process may take many clinical forms due to its capacity to affect vessels of different sizes (arteries, veins, and/or capillaries) and sites (involving either skin or internal organs), with a prognosis that may range from mild to life-threatening.[1,46] Current classification schemes recognise approximately 20 primary forms of vasculitis, with the most valid basis for classifying

Table 2. *The treatment of antiphospholipid syndrome*

Clinical situation		Treatment
Asymptomatic		Strict control of vascular risk factors: - smoking - hypertension - hypercholesterolaemia - oral contraception
		Observation and/or low-dose aspirin (75 to 150 mg)
		Hydroxicloroquine/cloroquine
Thrombosis	Deep venous – 1st event	Lifelong oral anticoagulant (INR 2-3)
	1st stroke	Lifelong oral anticoagulant (INR 2-3) and/or low-dose aspirin
	Transient ischaemia	Low-dose aspirin
	1st non-cerebral arterial event	Lifelong oral anticoagulant (INR 2-3) and low-dose aspirin
	Recurrent arterial/venous event	Indefinite amount of time / lifelong oral anticoagulant (INR 3-4) or LMWH
	Catastrophic APS	IV heparin IV high-dose steroids Plasma exchange or IVIG
Pregnancy	No previous history	Observation and/or low-dose aspirin
	Recurrent first trimester or second/third trimester foetal loss	LMWH and low-dose aspirin
Thrombocytopenia	Mild (100-150)	Observe
	Moderate (50-100)	Observe
	Severe (<50)	High-dose steroids, IVIG, rituximab

INR = international normalised ratio; LMWH = low-molecular-weight heparin; IVIG = intravenous immunoglobulins.

the vasculitides being the size of the predominant blood vessels involved (large, medium-sized, or small-vessel vasculitis).[47] However, in recent years there has been growing interest in classifying the clinical vasculitic syndromes into primary and secondary forms.[48] In the primary group, the primary pathology involves the blood vessels. In the secondary group, inflammation of blood vessels occurs as a complication of the underlying disease process (mainly systemic autoimmune diseases) or is triggered by exogenous factors such as drugs, infections, or neoplastic manifestations.

Whereas cutaneous vasculitis is the most common form of SLE vasculitis, visceral involvement is described in less than 10% of cases but can be life-threatening and require aggressive treatment.[49] SLE cutaneous vasculitis is presented by a wide spectrum of lupus nonspecific lesions, such as purpural, urticarial, and limb lesions, which can be both lymphocytic or leukocytoclastic infiltration types.[50] Visceral vasculitis in SLE mostly coincides with systemic flares and is frequently reported to occur following or in association with cutaneous vasculitis. Common types of SLE vasculitis are shown in *table 3*.

Vasculitis may manifest in as many as 56% of SLE patients throughout their life, in contrast to antiphospholipid syndrome which has a prevalence of 15%. Patients with vasculitis are mainly male and tend to be of younger age.[51] Antibodies against endothelial cells have been identified as a major endothelial cell cytotoxic effector and have been implicated in the pathogenesis of several

Table 3. *Common types of cutaneous and visceral vasculitis in SLE patients*

Cutaneous vasculitis	
	Punctate vasculitic lesions
	Palpable purpura
	Urticarial vasculitis
	Plaques and panniculitis
Visceral vasculitis	
	Central nervous system
	Peripheral nervous system
	Pulmonary vasculitis
	Gastrointestinal vasculitis
	Renal vasculitis
	Cardiac vasculitis
	Large vessel vasculitis

connective tissue diseases, predominantly vasculitides.[52] More than 80% of systemic lupus erythematosus patients are positive for antiendothelial cell antibodies (AECAs).[53] Other forms of SLE-related vasculitis include drug-induced vasculitis[54] and infection-induced vasculitis[55] either through direct compromise of the vascular wall by pathogens, or through antigen-induced autoimmune and inflammatory processes. Some drugs may play a role in the induction of inflammatory vascular lesions in SLE. The drug molecule may act as a hapten, which as a result of autoantigen binding alters the antigen properties. Some of the SLE-inducing drugs are: penicillins, allopurinol, thiazides, pyrazolones, retinoids, streptokinase,

cytokines, monoclonal antibodies, chinolons, hydantoin, carbamazepine and other anticonvulsants.[1,56] Vasculitis may be a result of a direct attack of microorganisms on the blood vessel wall or may be caused by infected thrombotic mass.[16] Hepatitis C virus may take part in vasculitis development, with the cryoglobulin presence.[57] There is an unexplained relationship between blood cryoglobulins and hepatitis C.[16] The following mechanisms leading to viral and bacterial vasculitis in SLE have been suggested: 1) the viruses directly attack the vascular wall inducing an inflammatory process, 2) some of them, as cytomegalovirus, may permeate and activate endothelial cells leading to vasculitis and 3) bacterial *Staphylococcus* antigens, as for example neutral phosphatase, may bind with basement membranes and adhere specifically to IgG, which in turn induces an immune response and an inflammatory process.

Vasculitis is among the most characteristic processes involved in the cutaneous and visceral expression of SLE. The development of vasculitis in SLE is of prognostic value. Reduction of SLE activity and prevention of flares (which are partly due to vasculitis) is the key point of treatment. Cutaneous SLE vasculitis is successfully treated with antimalarial agents. The discontinuation of antimalarial agents is clearly associated with an increased risk of both skin vasculitis and systemic SLE flares.[58] Thalidomide was reported to improve cutaneous lupus erythematosus, especially when antimalarial agents were unsuccessful in achieving remission of cutaneous lupus erythematosus or cutaneous vasculitis.[59] Dapsone, known for its antimicrobial properties, is also an immunomodulatory agent that is effective in the treatment of cutaneous vasculitis in SLE.[60] SLE is generally treated with glucocorticoids in combination with some steroid-sparing agents. In the treatment of visceral forms of SLE vasculitis cyclophosphamide and azathioprine are the two most commonly used cytotoxic immunosuppressive agents.[61] If there is major organ involvement, these medications, in combination with corticosteroids, need to be employed early in order to prevent or minimise irreversible damage. Many studies have shown the benefit of intravenous immunoglobulin in suppressing SLE flares and controlling and treating visceral vasculitis.[62] Recently mycophenolate mofetil has been introduced in the treatment of SLE and seems to be effective in controlling global disease activity even when other therapeutic regimens have failed.[63] However, few studies on the use of mycophenolate mofetil in the treatment of refractory cutaneous lupus erythematosus are available and their results are controversial.[64] Based on knowledge of the different dysregulated immunological pathways involved in SLE pathogenesis, specific targeted therapies have been developed. Rituximab is currently not an approved agent for the treatment of SLE. Nevertheless, in refractory SLE patients the addition of rituximab to the immunosuppressive treatment (as an off-label drug) may be considered.[65] Belimumab is a human monoclonal antibody that inhibits B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS) and it is approved for the treatment of mild-to-moderate SLE.[66,67]. Belimumab should be considered in SLE patients with visceral vasculitis who are refractory to various combinations of immunosuppressives/immunomodulators agents.

CONCLUSION

Vascular involvement in SLE, either as a direct complication of the disease or developing as an accompanying comorbidity, significantly impairs the quality of life of SLE patients and represents the most frequent cause of death.[68] Vascular involvement in SLE may be of inflammatory or thrombotic origin.[1] Both mechanisms involve the immune system, and the activation and consequent endothelial lesions play a very important role in disease pathogenesis.[1,69] It seems that endothelial cell activation with pronounced expression and activation of adhesive molecules are the key factors in the pathogenesis of this disease.[19,69] Activated endothelial cells are able to bind various proteins and cells to the vessel wall. This process is at first limited only to postcapillary venules, which are often affected in the small vessel disease. However, vasculitis localisation in arterial branching is most probably the result of compression forces.[19] The damage localisation may also depend upon the hydrostatic pressure values and local blood circulation disorders.

Understanding of the vascular abnormalities and the underlying pathogenic process is clearly important for providing new insights into the treatment of SLE. Continued research into the mechanisms of lupus-related vascular involvement will hopefully provide effective tools and targets to improve their survival and overall quality of life.

CONFLICT OF INTEREST

None

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REVIEW

Primary symptomatic adrenal insufficiency induced by megestrol acetate

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ABSTRACT

Megestrol acetate (MA) is a progestational agent for the treatment of metastatic breast cancer and endometrial cancer. MA has also been used to promote weight gain in malnourished elderly patients, in patients with immunodeficiency virus and in cancer-induced cachexia. In addition to thromboembolic disease, MA may induce hyperglycaemia, osteoporosis, suppression of the gonadal axis, and Cushing's syndrome. MA has also been shown to cause symptomatic suppression of the hypothalamic-pituitary-adrenal (HPA) axis owing to its intrinsic glucocorticoid-like effect. Three additional patients are presented who developed symptomatic adrenal insufficiency while they were receiving 160-320 mg MA daily. The patients were treated with cortisone acetate supplements, had clear evidence of HPA-axis suppression but recovered fully after MA was discontinued. Patients receiving MA might have an inadequate adrenal response during stressful conditions, possibly because 160-320 mg MA daily may not provide adequate protection to prevent the symptoms of adrenal insufficiency. The adverse MA effect on the HPA axis is probably not well recognised in clinical practice, and clinicians need an increased awareness of the endocrine complications secondary to MA treatment.

KEYWORDS

Adrenal insufficiency, failure to thrive, megestrol acetate

INTRODUCTION

Megestrol acetate (MA) is a synthetic progestin that has been used for the treatment of breast cancer, advanced endometrial carcinoma and, subsequently, as second-line hormone therapy in advanced stages of other neoplastic diseases. Since the drug promotes weight gain, MA is frequently used for stimulating appetite in patients with wasting illnesses, including patients with cancer-associated anorexia and human immunodeficiency virus.

Multiple side effects have been reported in relation to the chronic use of MA, including hyperglycaemia and thromboembolic events. Chronic administration of MA has also been reported to induce Cushing's syndrome together with suppression of the hypothalamic-pituitary (HPA) axis. The mechanisms underlying these MA effects are thought to be mediated by the inherent glucocorticoid activity of progesterone and its derivatives. In particular, MA displayed considerable affinity toward the glucocorticoid receptors, which was significantly greater than that of the naturally occurring ligand cortisol. Although these pharmacological properties of MA may explain the majority of its side effects, the impact of the drug on the HPA axis still represents a clinical problem which should alert physicians to the possibility of adrenal suppression in patients taking MA.

Our case series identifies three symptomatic cancer patients who were being treated with MA, who presented with severe adrenal insufficiency (*table 1*).

PATIENT 1

An 81-year-old man with a past history of prostate cancer treated with prostatectomy, medical castration and chemotherapy was admitted to the hospital for suspected pneumonia. His medications included MA at a dose of 160 mg/daily for one year, oxycodone, ramipril, furosemide, and spironolactone.

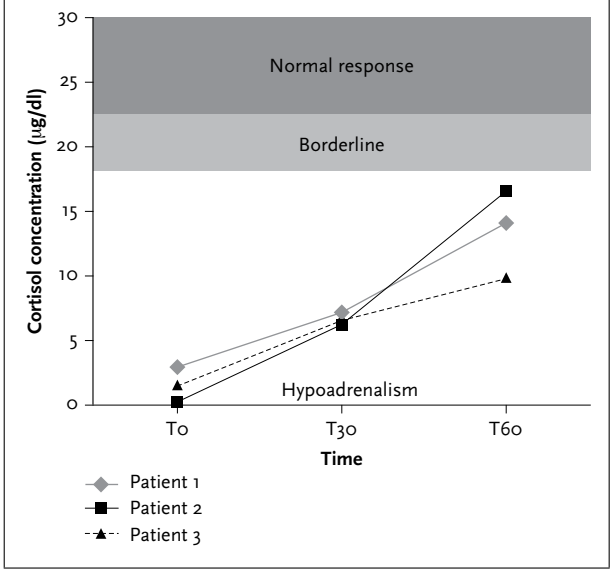
Blood count revealed megaloblastic anaemia (haemoglobin (Hb) 10.8 g/dl with a reference range of 13.1-17.1) due to

Table 1. *Summary of main features of the three case reports*

	Patient 1	Patient 2	Patient 3
Age (years)	81	70	70
Sex	Male	Female	Female
Disease	Prostate cancer	Breast cancer	Breast cancer
Dose of MA	160 mg/ daily	160 mg/ daily	320 mg/ daily
Duration of therapy	1 year	2 weeks	5 months
ACTH, pg/ml (10-60)	10	5	8
Cortisol, µg/ dl (3.7-19.4)	< 0.5	0.3	1.6
TSH, µUI/ml (0.35-4.94)	1.58	0.61	1.2
LH, mUI/ml (3.1-36.4)	0.07	11.47	14.2
FSH, mUI/ml (1.5-9.3)	2.11	21.5	18.5
Prolactin, ng/ml (2.58-18.12)	13.02	16.02	15.04

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH = luteinising hormone; MA = megestrol acetate; TSH = thyroid-stimulating hormone.

Figure 1.



folic acid deficiency and mild leukocytosis. Blood tests showed hyponatriaemia (129 mEq/l with a reference range of 135-145), The patient was treated with fluid replacement and broad spectrum intravenous antibiotics, as a chest X-ray was consistent with the diagnosis of pneumonia. Additional laboratory testing revealed undetectable morning cortisol and adrenocorticotropic hormone (ACTH) levels, low luteinising hormone, and low total and free testosterone. Follicle-stimulating hormone, thyroid-stimulating hormone, and prolactin were normal. Low-dose cosyntropin stimulation test revealed an inadequate adrenal response (*figure 1*). We also performed magnetic resonance imaging (MRI) of the pituitary, which was normal. We discontinued MA and replaced it with cortisone acetate 25 mg in the morning and 12.5 mg in the afternoon. After a few days the patient reported progressive improvement of the symptoms and disappearance of the fever. Chest X-ray confirmed that the pneumonia had resolved.

PATIENT 2

A female patient was admitted to our ward for severe asthenia, and weight loss. She had a clinical history of invasive ductal carcinoma of the left mammary gland treated with surgical removal of the upper outer quadrant, local radiotherapy, and adjuvant hormonal therapy. No tumour relapse occurred during the follow-up period of 20 years since the original diagnosis. Two weeks before admission to the hospital she started MA 160 mg daily for weight loss despite reported appropriate food intake. The physical examination revealed a low weight (36.5 Kg) with a body mass index (BMI) of 15.8 kg/m^2. Initial laboratory tests were normal with the exception of decreased Hb (10.4 mg/dl) and low ACTH (5 pg/ml with a reference range of 10-60) and cortisol (0.3 µg/dl, normal value 3.7-19.4). Low-dose cosyntropin stimulation test was consistent with adrenal insufficiency, as cortisol reached a value of 164.88 ng/ml 60 minutes after infusion. The other pituitary hormones were all in the normal range for age and sex. Antibodies against 21 hydroxilase were negative as well. The MRI of the pituitary was normal. We discontinued MA and prescribed cortisone acetate 25 mg in the morning and 12.5 mg in the afternoon. The patient reported improvement of the asthenia after just a few days. Three months later cortisone acetate was discontinued and cortisol and ACTH were both in normal range.

PATIENT 3

A 70-year-old woman was admitted to the hospital for evaluation of profound fatigue, decreased appetite and light-headedness on standing. She had undergone surgery for ductal carcinoma of the left breast three years previously, which was treated by mastectomy, axillary lymph node resection with adjuvant chemoradiotherapy. Approximately five months before hospitalisation she was started on MA 320 mg/day to stimulate her appetite and improve her nutrition. Laboratory tests were normal with the exception of mild hyponatraemia (130 mEq/l). Approximately 24 hours after admission, the patient developed worsening fatigue, nausea and became hypotensive. Infectious, cardiac, and neurological causes for hypotension were ruled out;

suspecting adrenal insufficiency, baseline cortisol serum levels were determined (1.6 µg/dl) and a low-dose cosyntropin stimulation test was performed. Cortisol levels 30 and 60 minutes after stimulation were 6.8 and 10 µg/dl, respectively, indicating a suboptimal adrenal response. ACTH level was 8 pg /ml. Normal saline and hydrocortisone (50 mg iv every six hours) was started with marked improvement of clinical parameters including blood pressure. MRI studies of the pituitary were then carried out, which showed no abnormalities of pituitary anatomy. The patient was discharged home on cortisone acetate taper, which was progressively reduced and finally discontinued with normalisation of ACTH and cortisol plasma levels.

DISCUSSION

MA is a synthetic progestin agent that has been used as second-line treatment for advanced endometrial and breast cancer,[1] although the exact mechanism of its antitumoral action is not known. More recently, its use has been suggested to reduce flushes in postmenopausal women, and in males with prostate cancer.[2,3] MA might act through a reduction of plasma oestrogen induced by MA-mediated inhibition of gonadotropin, although discordant data have been reported.[4]

An additional hypothesis suggests that MA might alter oestrogen metabolism via a downregulation of oestrogen receptors.[5-7] MA, at the dose of 400-800 mg per day, has been used increasingly in the treatment of cachexia related to AIDS and disseminated cancer, resulting in an increase in appetite and sustained weight gain.[8,9] MA may increase fat mass, mainly at the central level, without modifying body water content or lean mass.[10,11] This is the most common effect, although a few patients did not display weight gain. This possibility is more frequent in patients with AIDS, particularly in patients with lower $CD4^+$ counts and more severe disease.[10].

MEGESTROL ACETATE AND GLUCOCORTICOID ACTIVITY

High doses or a prolonged treatment period with MA have been reported to produce a clinical appearance of Cushing's syndrome and to reduce plasma ACTH and cortisol secretion, leading to adrenal insufficiency secondary to prolonged suppression of the HPA axis. This action of MA on the HPA axis is currently attributed to the glucocorticoid-like activity of the drug. The affinity of MA for the glucocorticoid receptor was shown in the 1980s by Kontula *et al*. who demonstrated that MA displayed affinity to glucocorticoid receptors of human mononuclear leucocytes, with a binding capacity of 46% as compared with the reference compound dexamethasone. The affinity of MA was notably greater than that of the natural ligand cortisol, which had a relative binding affinity of only 25%. The authors concluded that MA possessed inherent glucocorticoid activity, and that it could alter cortisol synthesis by suppressing HPA axis when used in humans.[12]

MEGESTROL ACETATE AND PITUITARY-ADRENAL AXIS

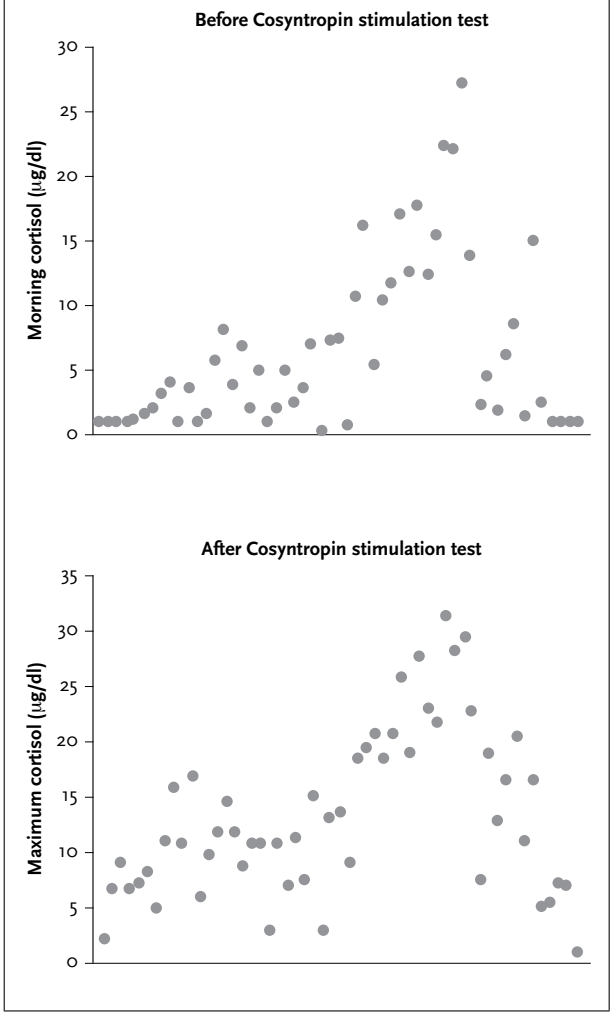
The effect of MA on cortisol secretion in humans was first demonstrated by Alexieva-Figusch *et al*.[4]. Some years later, Loprinzi *et al*. reported that patients taking MA at doses of 160 mg or 800 mg daily had low blood cortisol and ACTH levels.[13] Leinung *et al*. confirmed these data and demonstrated that before starting MA therapy patients had normal ACTH and cortisol values, both basal and after low-dose cosyntropin stimulation test. After at least a month of therapy (240 mg/day), plasma ACTH and cortisol levels showed a decrease together with a reduced adrenal response to cosyntropin stimulation.[14] Naing *et al*.[15] performed three different tests in ten post-menopausal women receiving MA in order to investigate the hypothalamic or pituitary site of MA action. Most patients had a normal response to the cortisol-releasing hormone test, demonstrating a possible suppression of the axis at the hypothalamic level, although a small number of patients showed no response. So there is still some doubt as to whether MA-induced suppression occurs at the level of the hypothalamus and/or at the pituitary gland. The clinical impact of the pharmacological effect of MA is still unknown since these patients may have no symptoms in baseline conditions, although they are known to have an abnormal activation of adrenal secretion under stressful situations. Moreover, cortisol suppression may well occur during both chronic and acute administration.[16] The suppression of the HPA axis induced by MA is not sex and age dependent.[14,17,18] It has been postulated that MA could have two different activities on glucocorticoid receptors: weak agonist initially, and then acting as an antagonist by blocking more potent glucocorticoid. Consistent with this hypothesis, adrenal insufficiency was described in patients currently taking MA and in those who abruptly discontinued it after prolonged use. This evidence, taken together, clearly suggests that the endocrine effects observed *in vivo* during MA therapy are caused by the glucocorticoid-like activity of the compound.

In our cases, all the patients were being treated with MA. ACTH and cortisol levels were below the reference range, and the corticotropin-stimulation test confirmed

the presence of adrenal insufficiency, probably caused by chronic ACTH suppression. We could not perform further dynamic endocrine tests in these patients owing to the severity of their clinical conditions. However, MRI studies excluded adrenal insufficiency secondary to pituitary abnormalities in Patient 1 as well as in Patient 2. Moreover, in Patients 2 and 3 a normal adrenal function after discontinued MA was documented. Therefore, the clinical and biochemical data of our report clearly suggest that the HPA insufficiency was likely caused by MA therapy. Our case series also raises the additional question as to whether the glucocorticoid activity of MA can provide adequate protection to prevent the symptoms of adrenal insufficiency, particularly in stressful conditions.

Previously published data and a MEDLINE search (1980-2012) performed by us, demonstrated that in patients taking MA morning cortisol levels can be suppressed, defined by a morning cortisol level of <5 μg/ dl, with a prevalence ranging from 33% to 90%. Cortisol levels are always low with MA 800 mg/daily dosing and they may even be lower with a 160 mg/ daily dose. From a clinical standpoint, few patients were reported to be overtly symptomatic. However, the symptoms of hypoadrenalism (anorexia, nausea, fatigue) have low specificity since they are commonly reported by cachetic patients with cancer and/or AIDS, meaning that adrenal insufficiency is often overlooked, left undiagnosed, and might be fatal in compromised patients. Furthermore, patients who are biochemically hypoadrenal during MA-induced suppression of the HPA axis might, although clinically asymptomatic, have relative adrenal insufficiency in the presence of stressful conditions, such as sepsis, burns, and major surgery. ACTH and cortisol level in the morning should be checked together with 24-hour urinary free cortisol value in all patients taking MA, even if asymptomatic, and a corticotrophin-stimulating test performed, since using only the morning cortisol value may underestimate the frequency of hypoadrenalism (*figure 2*). The diagnostic use of low-dose ACTH stimulation may reveal mild adrenal insufficiency that would be missed with the standard high-dose pharmacological test.[19] Although not universally accepted, the low-dose corticotropin test seems to be superior to the standard-dose test for diagnosing chronic HPA insufficiency.[20]

Figure 2. *Overview of reported cases of Cosyntropin stimulation test in patients taking MA. The overall frequency of hypoadrenalism was 58% before and 73% after the test*



MEGESTROL ACETATE AND OTHER ENDOCRINE COMPLICATIONS

MA can also alter the secretion of other pituitary hormones, including a decrease in gonadotropin, testosterone and oestrogen secretion and a mild elevation in plasma prolactin levels. The low testosterone plasma level observed in Patient 1 confirms previously published data. This additional action of MA leading to androgen deficiency in males may represent a real clinical problem, particularly when MA is mainly prescribed to treat anorexia and weight loss.

MA can adversely affect bone metabolism. Well-documented cases of osteoporosis probably induced by MA chronic therapy have been reported.[21] The glucocorticoid activity of MA was probably the causative factor although the reduction of oestradiol and testosterone production induced by a MA-mediated gonadotropin suppression may represent an additional variable.

As for its glucocorticoid-like activity, MA could eventually result in the other typical complications of corticosteroids therapy. In the literature, some cases of Cushing's syndrome in association with the use of MA have been reported.[22] They were correlated with high doses and

long-lasting duration of the therapy. Hyperglycaemia and diabetes mellitus could occur as well, but their clinical appearances were usually precocious and often manifest with doses of MA that were lower than those causing Cushing's syndrome.

In conclusion, recognising MA activity on the HPA axis is clinically important for the diagnosis of subclinical hypoadrenalism or overt adrenal insufficiency, particularly when the therapy is discontinued. Moreover, symptomatic adrenal failure can occur during MA administration, as documented by published case reports and by our additional patients, suggesting that supplementation of hydrocortisone seems to be empirically indicated for major surgery or stressful situations. Finally, the glucocorticoid-like activity of MA should be kept in mind during chronic therapy, since hyperglycaemia, clotting disorders, osteoporosis, hypogonadism as well as Cushing's syndrome have been clearly documented in clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Course of HbA1c in non-diabetic pregnancy related to birth weight

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ABSTRACT

Background: Despite good glycaemic control (according to the internationally accepted level of HbA1c < 7% (53.0 mmol/mol)) the incidence of macrosomia in pregnant women with diabetes is still very high. We measured HbA1c levels in each of the three trimesters of pregnancy in a cohort of healthy women to determine whether the upper reference level for good glycaemic control in diabetic pregnant females should be lower than the internationally accepted level. Secondly we investigated whether changes in HbA1c values in the course of pregnancy are associated with birth weight.

Methods: We determined HbA1c by high-performance liquid chromatography in 103 healthy pregnant women. The results were corrected with a method which was certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the Diabetes Control and Complication trial reference assay. All women had a body mass index (BMI) < 30, none of the women had diabetes in the family in the first and/or second degree. The multiparous women had no history of macrosomia or small for gestational age infants.

Results: In the first trimester mean ± SD (range) HbA1c (n=93) was 4.7 ± 1.25% (27.9 ± 13.7 mmol/mol) (3.9-5.4% (19.1-35.5 mmol/mol)), in the second trimester (n=86) 4.6 ± 1.33% (26.8 ± 14.6 mmol/mol) (3.7-5.7% (16.9-38.8 mmol/mol)) and in the third trimester (n=71) 4.9 ± 1.39% (30.1 ± 15.2 mmol/mol) (4.0-6.0% (20.2-42.1 mmol/mol)). The calculated upper reference HbA1c values for the three trimesters were 5.4, 5.5 and 5.8% (35.5, 36.6 and 39.9 mmol/mol), respectively, compared with 6.5% (47.5 mmol/mol) in non-pregnant women in our hospital. We found a significant correlation between the differences of the first and second trimester HbA1c values and the birth weight percentiles (r=-0.251; p=0.032). All 44 women with a decrease in the HbA1c value from the first to the second trimester had a birth weight percentile ≤90. In the 30 women with no change or an increase in the HbA1c value from the first to the second trimester there was no relation between HbA1c values and birth weight percentiles, but seven of the 30 (23.3%) had a birth weight percentile of > 90.

Conclusions: HbA1c is lower in all three trimesters of normal pregnancy compared with the level in non-pregnant women, and the change in HbA1c from the first to the second trimester predicts (the percentile of) birth weight. This could implicate that in order to prevent macrosomia in pregnant women with diabetes one should aim at lower HbA1c levels than the internationally accepted level, and at a decrease in HbA1c from the first to the second trimester.

KEYWORDS

HbA1c, pregnancy, birth weight

INTRODUCTION

Despite good glycaemic control according to the internationally accepted level of HbA1c < 7% (53.0 mmol/mol) before and during pregnancy,[1] the incidence of macrosomia in women with diabetes is still very high: 48.8%.[2] Studies disclose that HbA1c levels in healthy females are lower in pregnant than in non-pregnant women.[3] Mosca *et al.*[4] reported in a population of 445 pregnant women without diabetes and in a control group of 384 non-pregnant women a lower range in pregnant women (4.0-5.0% (20.2-31.1 mmol/mol)) than in non-pregnant women (4.8-6.2% (29.0-44.3 mmol/

mol)). This might implicate that the accepted HbA1c level in pregnancy for the prevention of macrosomia is too high. However, studies show a discrepancy in the course of HbA1c levels during the three trimesters of pregnancy. Worth *et al.*[5] and Hashimoto *et al.*[6] found an increase, Hartland *et al.*[7] and O'Kane *et al.*[8] reported no significant change, and Hanson *et al.*[9] and Gunter *et al.*[10] found a decrease. In a recent Japanese study Hiramatsu *et al.*[11] determined HbA1c in 574 pregnant and 32 non-pregnant, healthy women. HbA1c was significantly lower in the second (mean 4.9% (30.1 mmol/mol)) than in the first trimester (mean 5.2% (33.3 mmol/mol)). Mean HbA1c in the third trimester and in non-pregnant women was also 5.2% (33.3 mmol/mol), but the difference with the second trimester was not significant. The reference intervals for the groups were: 4.4-5.4% (24.6-35.5 mmol/mol), 4.7-5.7% (27.9-38.8 mmol/mol), 4.6-5.8% (26.8-39.9 mmol/mol) and 4.8-5.6% (29.0-37.7 mmol/mol), respectively.

There are several reports about the most important trimester concerning diabetic control in relation to birth weight. Gold *et al.*[12] showed that birth weight, corrected for gestational age, is best correlated with the HbA1c of 0-12 weeks of gestational age in women with type 1 diabetes. Page *et al.*[13] also suggest that macrosomia may be reduced by tighter control of diabetes at conception and in the first trimester but to a lesser extent during later stages of pregnancy. Mello *et al.*[14] found that only overall daily glucose values ≤ 95 mg/dl throughout the second and third trimesters can avoid alterations in foetal growth. Kerssen *et al.*[15] reported that in a group of women with type 1 diabetes extremely large for gestational age (LGA) infants at birth were already large before the 30th week of gestation. In these early LGA infants (foetal growth parameters ≥ 95 percentile at ≤ 30 weeks of gestation and birth weight percentile > 90), the second trimester median glucose level was significantly higher than those in the first and third trimester.

We studied a cohort of healthy, non-diabetic, pregnant women. We measured HbA1c in each trimester and investigated the influence of the change in Hba1c levels from one trimester to the other on birth weight percentiles.

MATERIALS AND METHODS

Patients

We investigated HbA1c levels in a group of healthy, pregnant women who visited the Department of Obstetrics of Leiden University Medical Centre for antenatal care between November 2002 and October 2004. The study was approved by the Ethics Committee of Leiden University Medical Centre. All subjects gave written informed consent. Excluded were women with: a body mass index (BMI) before pregnancy of ≥30, diabetes mellitus, a family history of diabetes in the first and/or second degree, hypertension, known lipid disorders, renal disease, use of corticosteroids, recurrent abortion, a history of large for gestational age (birth weight ≥ 4000 gram) and of small for gestational age infants, pre-eclampsia, preterm birth (< 34 weeks) and/or a stillbirth in a previous pregnancy. From the 130 included women, 27 (mean ± SD age: 31.9 ± 5.5 years and mean ± SD BMI (n=15): 22 ± 3) had to be withdrawn from the study: 7 due to twin pregnancy, 3 due to missed abortion, 3 due to very preterm delivery, 2 due to transfer to another hospital after the first visit and one due to termination of pregnancy because of trisomy 21. Although included, 11 women had no HbA1c measurements taken at all. Nine women were of non-Caucasian origin, but their characteristics were similar to the whole group.

HbA1c levels were measured in each trimester of pregnancy in the remaining 103 women (mean ± SD age: 31.4 ± 5.2 years and mean ± SD BMI (n=90): 23 ± 3): between 10-14 weeks, between 24-26 weeks and between 34-36 weeks in the first, second and third trimester of pregnancy, respectively. From the patients who did not complete the three measurements 7 delivered preterm, and in 39 cases blood was not sampled for logistic reasons. Overall, 57 women had three values measured, 34 two and 12 only one. HbA1c values of one woman (4.5, 4.7 and 5.4% (25.7, 27.9 and 35.5 mmol/mol), respectively) were kept out of the analysis, because she had a severely dysmature baby due to multiple congenital malformations at birth.

Between 32-36 weeks an ultrasound was performed to determine foetal growth parameters. Macrosomia was diagnosed in case of a discrepancy between foetal head (HC) and abdominal circumference (FAC) measurements: HC conform P50 and FAC > P90.

Records were kept of gestational age at time of delivery, birth weight, birth weight percentile (according to Dutch growth charts[16]), sex, mode of delivery and complications during delivery.

Analysis

We determined HbA1c levels by high-performance liquid (cation exchange) chromatography. The results were corrected with those of a boronate affinity chromatography method which was certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the Diabetes Control and Complication trial reference assay.[1] The HbA1c level is given in % and SI units (mmol/mol). Pearson correlation coefficient was used to compare HbA1c levels in each trimester with birth weight percentiles. We calculated differences in HbA1c level between the first and second trimester, the first and third trimester, and the second and third trimester. We compared those differences with birth weight percentiles using the Pearson correlation coefficient.

RESULTS

HbA1c levels were normally distributed in each trimester. In the first trimester mean ± SD (range) HbA1c (n=93) was 4.7 ± 1.25% (27.9 ± 13.7 mmol/mol) (3.9-5.4% (19.1-35.5 mmol/mol)), in the second trimester (n=86) 4.6 ± 1.33% (26.8 ± 14.6 mmol/mol) (3.7-5.7% (16.9-38.8 mmol/mol)) and in the third trimester (n= 71) 4.9 ± 1.39% (30.1 ± 15.2 mmol/mol) (4.0-6.0% (20.2-42.1 mmol/mol)). In the group that completed the three measurements (n=57), the values were identical: in the first trimester 4.7 ± 1.24% (27.9 ± 13.6 mmol/mol) (3.9-5.3% (19.1-34.4 mmol/mol)), in the second trimester 4.5 ± 1.28% (25.7 ± 14.0 mmol/mol) (3.7-5.4% (16.9-35.5 mmol/mol)) and in the third trimester 4.8 ± 1.35% (29.0 ± 14.8 mmol/mol) (4.0-6.0% (20.2-42.1 mmol/mol)). We calculated the reference interval by taking the mean ± 2 x SD which includes > 95% of all measurements. The reference interval was 4.2-5.4% (22.4-35.5 mmol/mol) for the first, 3.9-5.5% (19.1-36.6 mmol/mol) for the second and 4.1-5.8% (21.3-39.9 mmol/mol) for the third trimester.

The distribution of birth weight percentiles was normal. We found no correlation between BMI before pregnancy, HbA1c value in each trimester and birth weight percentile (*table 1*).

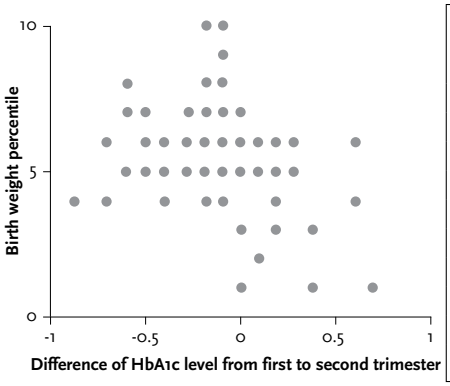
There was a significant correlation between differences of the first and second trimester HbA1c values and birth weight percentiles (*table 1*: r=-0.251; p=0.032; *figure 1*). We found no correlation between differences of the first and third trimester and of the second and third trimester HbA1c levels and birth weight percentiles (*table 1*). All 44 women with a decrease in HbA1c from the first to the second trimester had a birth weight percentile ≤ 90. In the 30 women with no change or an increase in HbA1c from the first to the second trimester, no relation was found between HbA1c and birth weight percentile, but seven of 30 infants (23.3%) had a birth weight percentile of > 90 (*table 2*).

Table 1. *Pearson correlation of different parameters with birth weight percentiles*

Parameters	Pearson correlation coefficient	p (2 tailed)
BMI (before pregnancy)	0.139	0.206
HbA1c 1st trimester	-0.030	0.978
HbA1c 2nd trimester	1.129	0.248
HbA1c 3rd trimester	-0.620	0.614
Difference 1st – 2nd trimester HbA1c	-0.251	0.032*
Difference 1st – 3rd trimester HbA1c	0.051	0.245
Difference 2nd – 3rd trimester HbA1c	0.151	0.696

***Correlation is significant at the 0.05 level (2 tailed).**

Figure 1. *Difference in % HbA1c levels from first to second trimester related to birth weight percentile*



Number	Birth weight percentile
10	≤ 2.3
9	> 2.3-5
8	> 5-10
7	> 10-25
6	> 25-50
5	> 50-75
4	> 75-90
3	> 90-95
2	> 95-97.5
1	> 97.5

Table 2. *Changes in HbA1c levels from first to second trimester related to birth weight percentiles*

Percentile	HbA1c decrease N (%)	HbA1c the same N (%)	HbA1c increase N (%)	Total N (%)
≤ 2.3	2 (100%)			2 (100%)
> 2.3-5	1 (100%)			1 (100%)
> 5-10	3 (100%)			3 (100%)
> 10-25	5 (71.4%)	1 (14.3%)	1 (14.3%)	7 (100%)
> 25-50	14 (56.0%)	3 (12.0%)	8 (32.0%)	25 (100%)
> 50-75	9 (60%)	3 (20.0%)	3 (20.0%)	15 (100%)
> 75-90	10 (71.4)		4 (28.6%)	14 (100%)
> 90-95		1 (33.3%)	2 (66.7%)	3 (100%)
> 95-97.5			1 (100%)	1 (100%)
> 97.5		1 (33.3%)	2 (66.7%)	3 (100%)
Total	44 (59.5%)	9 (12.2%)	21 (28.4%)	74 100%

All measurements were similar with and without those of the nine women of non-Caucasian origin in our sample.

All women had an ultrasound estimation of the foetal weight between 32 and 36 weeks. None of the ultrasounds showed signs of macrosomia.

DISCUSSION

We found a lower upper reference HbA1c level in each trimester of pregnancy compared with the upper reference

HbA1c value of 6.5% (47.5 mmol/mol) in non-pregnant, non-diabetic women in our hospital. The level increases from 5.4% (35.5 mmol/mol) in the first trimester and 5.5% (36.6 mmol/mol) in second trimester to 5.8% (39.9 mmol/mol) in the third trimester, but never reaches 6.5% (47.5 mmol/mol). These upper reference values indicate that the internationally accepted levels of good control for diabetic pregnant women (< 7% (53.0 mmol/mol)) may be too high. To our knowledge this is the first time that a relation between a change in HbA1c and birth weight has been found in healthy, non-diabetic, pregnant women. This means that change in HbA1c level as a reflection of change in mean blood glucose value from the first to the second trimester of pregnancy is an important determinant of the ultimate birth weight. The decrease in HbA1c from the first to the second trimester found by Hiramatsu *et al.*[11] supports the importance of our data. These findings could implicate that a change in glucose levels from the first to the second trimester of pregnancy is critical to prevent LGA and macrosomic babies in pregnant women with diabetes. Kerssen *et al.*[15] investigated a group of women with type I diabetes with a continuous glucose monitoring system (CGMS) to assess the relationship between 24-hour diurnal glucose profiles in all three trimesters of pregnancy and infant birth weight. The diurnal glucose profiles show that mothers of early LGA infants (< 30 weeks) had elevated glucose levels for most of the day during the second trimester ($p < 0.05$). Within the group of women with early LGA infants, the second trimester median glucose level was significantly higher than that in the first and third trimester. These data support our findings concerning the importance of the second trimester glucose level in preventing macrosomia at birth. However, a more tight glycaemic control in diabetic pregnancy goes hand in hand with an increasing incidence of severe hypoglycaemia, especially in the first trimester of pregnancy.[17]

We conclude that the upper reference levels of HbA1c in the three trimesters of pregnancy in healthy, non-diabetic women are lower (5.4, 5.5 and 5.8% (35.5, 36.6 and 39.9 mmol/mol), respectively) than the level of 6.5% (47.5 mmol/mol) in our hospital in healthy, non-pregnant women. The course of HbA1c during pregnancy, especially the change from the first to the second trimester, seems to be important in predicting birth weight.
Good glycaemic control in diabetic pregnancy before and in the first trimester of pregnancy is necessary for the prevention of congenital malformations.
Special attention may also be needed for the blood glucose level in the second trimester and the change in blood glucose from the first to the second trimester in preventing macrosomia. However, until now it is difficult to achieve this desired normoglycaemia in diabetic pregnancy without an increase in severe hypoglycaemia.
More investigation is needed to confirm that besides the absolute level of HbA1c, macrosomia in diabetic pregnancy is also related to a change in the course of HbA1c during pregnancy and especially to an increase in HbA1c from the first to the second trimester.

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Netherlands
The Journal of Medicine

CASE REPORT

Polyomavirus BK in the pathogenesis of bladder cancer

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ABSTRACT

Polyomaviruses are able to drive malignant transformation in rodent models, and have been implicated in the aetiology of a variety of human malignancies. However, the reports on this association in humans are strongly conflicting. Here we describe a renal transplant (RT) recipient with ureteral stenosis against the background of polyomavirus BK (BKV) activity. Six and a half years after transplantation, this patient developed metastasised bladder cancer. Prior to the diagnosis of cancer, atypical cells were detected in the urine that were denoted as 'decoy cells': virally infected epithelial cells that are frequently seen in the urine of RT recipients with BKV (re)activation, which may morphologically resemble malignant cells. Intriguingly, the primary urothelial carcinoma, as well as the mesenterial and two intestinal metastases, stained positive with antibodies against polyomavirus virus large T antigen protein, whereas the adjacent healthy tissue did not. This case suggests a role for BKV in the pathogenesis of bladder cancer, at least in the context of immunodeficiency.

KEYWORDS

Polyomavirus BK, bladder cancer, kidney transplantation, transforming viruses

INTRODUCTION

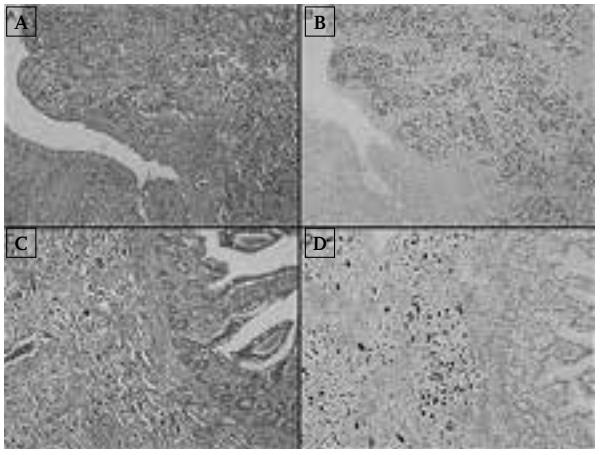
Polyomavirus BK (BKV) latently infects 70-100% of the human population but has not been associated with disease in immunocompetent individuals.[1] The most important site of latency is thought to be the urogenital tract. In immunocompromised renal transplant (RT) recipients, BKV frequently (re)activates, and may cause nephropathy (BKVN) and ureteral stenosis.[2] It has remained a topic of ongoing debate whether polyomaviruses are involved in the pathogenesis of human malignancies. Here, we report on the case of an RT recipient with active BKV replication who developed a metastasised bladder carcinoma. Both the primary tumour and the intestinal metastases stained positive with antibody against the Simian vacuolating virus 40 (SV40) large T antigen protein (LTAg), which cross-reacts with BKV- and polyomavirus JC (JCV)-LTAg.

CASE

A 56-year-old man of Caucasian ethnicity with end-stage renal disease due to polycystic kidney disease received a renal transplant from a living unrelated donor. Induction therapy consisted of anti-CD25 monoclonal antibody. Initial immunosuppressive treatment consisted of tacrolimus, mycophenolate mofetil and prednisolone, which was tapered to tacrolimus and prednisolone one year after transplantation. Four years after transplantation, he presented with high fever and pain over the transplant region. There was a drop in the Modification of Diet in Renal Disease (MDRD) score from 42 to 23 ml/min/1.73 m^2. Ultrasound examination and antegrade pyelography revealed hydronephrosis of the allograft due to a distal ureteral stenosis. Urine and blood cultures were positive for *Escherichia coli*. Plasma BKV viral load was high, mounting to 1.16 x 10^5 copies/ml as measured by large T antigen protein-PCR. In his urine, microscopic haematuria and cells with intranuclear inclusions and a high degree of

mitosis were seen. These cells were denoted as decoy cells consistent with BKV infection but urothelial malignancy could not be excluded (*figure 1*). A nephrostomy catheter was inserted, immunosuppressive therapy was tapered and antibiotic treatment was initiated. After an initial decline to undetectable levels, the viral load rose again to 1.69 x 10^4 copies/ml. Meanwhile, the patient developed two episodes of deep venous thrombosis of the calf veins and one arterial thrombosis of the iliac artery. The last two events occurred while using oral anticoagulation. Microscopic haematuria and decoy cells persisted, and cystoscopy showed an irregular papillary aspect of the posterior wall of the bladder. Biopsies revealed a high-grade urothelial carcinoma invading the bladder muscle and perivesicular fat. During surgery, extensive intraperitoneal and retroperitoneal metastases to the mesenterium and intestines became apparent. Ultimately, two years after detection of BKV infection, the patient died due to tumour progression. Remarkably, the primary tumour and the intestinal metastases but not the adjacent healthy tissue stained positive for SV40 LTAg (*figure 2*).

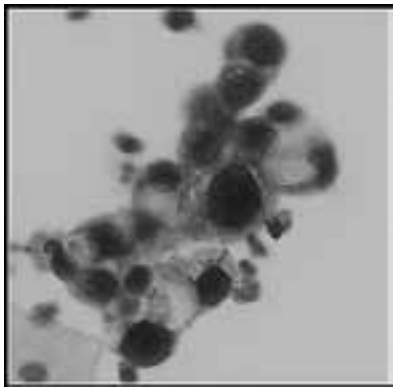
Figure 2. *Representative photographs of urothelial cell carcinoma of the bladder and small bowel metastasis of the patient described here. (A) The high-grade urothelial cell carcinoma shows a predominant nested growth pattern with infiltration in the lamina propria. (B) Immunohistochemical staining with an antibody against the SV40 T-antigen shows diffuse strong positive nuclear staining of the high-grade urothelial cell carcinoma. (C) Metastasis of the urothelial cell carcinoma in the small bowel wall shows extensive sarcomatoid dedifferentiation. (D) The SV40 T-antigen shows the same staining pattern in the small bowel metastasis as in the primary tumour. Original magnification x 50*



DISCUSSION

The patient described here presented with overt BKV replication four years after starting immunosuppressive medication. He was diagnosed with ureteral stenosis, a well-known complication of overt BKV replication.[2] Because there are no therapeutic agents that directly target BKV, immunosuppressive therapy was tapered to improve the patient's antiviral immune response.[3] The urinary decoy cells and microscopic haematuria were first considered to be compatible with BKV replication. Decoy cells are defined as enlarged nuclei with viral inclusions, owing to virus-induced DNA replication, and may indeed resemble malignant cells. Nevertheless, the finding of decoy cells is highly unspecific and they can be found in up to 42% of RT recipients.[4] Persistent haematuria and recurring thrombotic events strengthened the suspicion of malignancy, which was indeed found to be the case.

Figure 1. *Decoy cells in urine cytology preparation. Urine cytology specimen from our patient showing cells with enlarged nuclei with homogenised chromatin and possible nuclear ground-glass inclusions. Papanicolaou stain, 400 x original magnification*



The transforming potential of BKV and other polyomaviruses has long been recognised in rodent models. However, human cells are less prone to undergo transformation *in vitro* and conflicting literature on an association between polyomaviruses and various malignancies has only fuelled the debate.[2,5] Polyomaviruses possess several tools that promote malignant transformation of the host cell, amongst which a set of viral proteins produced early in the viral replication cycle, the T antigen proteins (TAgs).[2] Large TAgs can inhibit tumour suppressor protein p53 as well as retinoblastoma proteins.[6,7] This drives a cell towards replication, providing the virus with increased host transcription factors. Also the viral agnoprotein was shown to inhibit double-stranded DNA repair by negatively affecting the expression of Ku70 and Ku80 proteins.[8] Another mechanism may be the 'permissiveness' of cells to infection. BKV is thought not to complete its full replication cycle in non-permissive cells,

resulting in the transcription of only TAg proteins from the early region of the BKV genome.[2] Lastly, the BKV genome rearranges its non-coding control region (NCCR), altering the number and effectiveness of transcription factor binding sites and thereby also virulence and transforming potential. Such NCCR mutants have indeed been linked to certain urogenital malignancies.[9]

In this case, both the primary tumour as well as the distal intestinal metastases stained positive for LTAg, whereas the non-neoplastic tissue stained negative for LTAg. Perhaps, owing to tropism of BKV for urothelium, urothelial metastases are more susceptible to BKV infection in the setting of systemic BKV activity. Nevertheless, the adjacent non-neoplastic urothelium in the bladder was negative for LTAg staining (*figure 2B*). Publications on the association between BKV and bladder cancer are rare.[10,11] Larger series on an association of BKV or other polyomaviruses with bladder cancer vary greatly in their outcome and remain inconclusive. These differences in outcome may very well be explained by the different methods of detection used, ranging from BKV-LTAG, NCCR, VP1 PCRs to SV40 LTAg antibody staining on paraffin sections, and Papanicolaou staining on urine cytology specimens.[9,12-15]

CONCLUSION

Reports on an association between BKV and bladder cancer are rare, and the association between polyomaviruses and human malignancy is a topic of ongoing debate. Here, we convincingly show the presence of the viral transforming LTAg protein in the primary urothelial carcinoma and in the intestinal metastases, whereas the adjacent non-neoplastic tissue stained negative. Also since the intestines are normally not considered to be a niche for BKV infection, this case adds evidence for an implication of BKV in the pathogenesis of bladder cancer, a relation that may very well be more apparent in the context of immunodeficiency.

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CASE REPORT

Familial LCAT deficiency: from renal replacement to enzyme replacement

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ABSTRACT

Familial LCAT deficiency (FLD) is a recessive lipid disorder ultimately leading to end-stage renal disease (ESRD). We present two brothers with considerable variation in the age at which they developed ESRD. Kidney biopsies revealed both tubular and glomerular pathology. To date, no causal therapy is available, yet enzyme replacement therapy is in development.

KEYWORDS

Familial LCAT deficiency, FLD, LCAT, renal failure

What was known on this topic?
Familial LCAT deficiency (FLD) leads to end-stage renal disease (ESRD). No causal therapy is available to date.

What does this add?
We show considerable variation in the age at which ESRD occurs in FLD, demonstrate that FLD causes tubular pathology besides glomerular pathology, and discuss the development of enzyme-replacement therapy.

INTRODUCTION

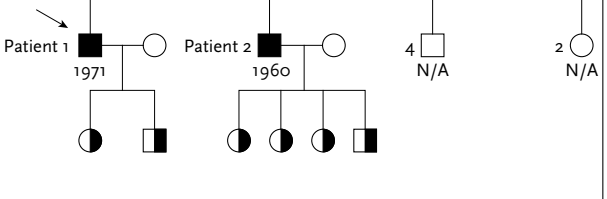
Patients with familial lecithin-cholesterol acyltransferase (LCAT) deficiency (FLD), a rare autosomal recessive disorder, are characterised by progressive corneal opacification, glomerulopathy, mild haemolytic anaemia and very low plasma levels of high-density lipoprotein cholesterol (HDL-c).[1] The molecular defect underlying FLD is homozygosity or compound heterozygosity for mutations in the gene encoding LCAT. LCAT is a pivotal enzyme in cholesterol metabolism, by virtue of its ability to esterify cholesterol molecules in HDL and low density-lipoprotein (LDL) particles, anchoring them in the lipophilic cores of these lipoproteins.[2,3]
With no causal therapy currently available, FLD patients often develop end-stage renal disease in the fourth decade of life.[4] Here, we describe FLD in two brothers of Turkish descent. One recently received a kidney transplant, the other developed severe renal insufficiency. The described cases illustrate the need for enzyme-replacement therapy, currently in preclinical development.[5]

CASE REPORT

Patient 1 was referred at the age of 25 because of generalised oedema. The patient had bilateral corneal opacification. Upon physical examination signs of lung oedema were noted. Blood pressure was 140/95 mmHg. Clinical characteristics are depicted in *figure 1*. Blood sample analysis revealed increased glomerular filtration and hypoalbuminaemia, complete HDL-C deficiency and low apolipoprotein A-I. In addition, a mild microcytic anaemia was shown. Proteinuria was noted in the absence of leucocyturia or erythrocyturia. Upon ultrasonography, no structural renal abnormalities were found.

Quinapril, furosemide and candesartan were started, resulting in resolution of the oedema and a decrease in proteinuria and renal clearance (12.4 g/l to 9.4 g/l and from 165 ml/min to 130 ml/min). Notwithstanding, the

Figure 1. *Pedigree of FLD patients*



	Patient 1	Patient 2
Albumin:	14 g/L	47 g/L
eGRF	165 mL/min	28 mL/min
Haemoglobin	7.0 mmol/L	7.6 mmol/L
MCV	78 fL	93.3 fL
Urine protein	12.4 gr/L	++
TC	5.7 mmol/L	3.6 mmol/L
LDL-C	2.2 mmol/L	1.02 mmol/L
HDL-C	< 0.10 mmol/L	0.12 mmol/L
TG	7.1 mmol/L	5.47 mmol/L
Apo A-I	0.38 g/L	--
Apo B	0.30 g/L	--

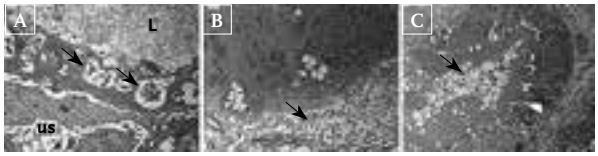
Squares are males, circles females; arrow in pedigree indicates proband. Filled symbols indicate homozygotes for LCAT^{T345M}, half-filled symbols indicate heterozygotes. Four brothers and two sisters of the patients were not available for analysis (N/A). eGFR = estimated glomerular filtration rate; MCV = mean corpuscular volume, TC = total cholesterol; LDL-C = low density lipoprotein-cholesterol; HDL-C = high density lipoprotein-cholesterol; TG = triglycerides; Apo A-I = apolipoprotein A-1; Apo B = apolipoprotein B.

patient developed ESRD at the age of 37. His brother – Patient 2, 50 years old – was evaluated as a kidney donor, but upon assessment he was shown to suffer from corneal opacification, HDL-C deficiency and severe proteinuria as well.

Electron microscopy of a renal biopsy of Patient 1 showed accumulation of electron-lucent vacuoles with or without osmiophilic particle cores in the glomerular basement membrane, Bowman's capsule, the tubular basement membrane and the lumen of tubules. Segmental foot process effacement, foam cell accumulation in the mesangium and a distorted architecture of the glomerular and tubular basement membrane were also noted (*figure 2*).

The patients' parents were first cousins (*figure 1*), and the presence of FLD as underlying disease was anticipated. Plasma LCAT activity, measured as the ability of plasma LCAT to esterify free cholesterol in proteoliposomes,[6] was severely reduced in both patients: 0.75 nmol cholesterol ester/h/ml (normal: 25 nmol/h/ml). Upon DNA analysis,[3] both patients were found to be homozygous carriers of an ACG→ATG mutation in exon 6, resulting in the p.T345M substitution in LCAT.[7]

Figure 2. *Electron microscopy of renal biopsy of patient 1*



A: Glomerulus. Glomerular basement membrane with accumulation of lipids. US: urinary space, L: capillary lumen, arrows: osmiophilic structures.
B: Tubular basement membrane with osmiophilic structures (arrow).
C: Tubule. L: Lumen with osmiophilic structures (arrow).

DISCUSSION

Here we report familial LCAT deficiency (FLD) in two brothers of Turkish descent. We show that the age at which end-stage renal disease develops is variable and we also demonstrate that renal pathology in FLD is not only characterised by glomerular changes, but also by profound tubular changes.
To date, 88 mutations in *LCAT* have been described.[8] Severe mutations lead to complete inactivation of the LCAT enzyme, and consequentially to FLD. The T345M mutation identified in our two patients was originally described in a Sardinian patient.[7] The threonine residue at position 345 is conserved up to C. elegans, but it is currently unknown why this specific residue is crucial for normal enzyme function.

Patients with FLD suffer from progressive proteinuria and renal dysfunction, on average leading to ESRD in the fourth decade of life.[1] Patient 1 indeed developed ESRD at the age of 37, but Patient 2, his full brother, was 50 years old when severe renal insufficiency was noted during a work-up for renal transplantation. The reason for the variable course of renal disease progression in our two FLD patients is unknown and remarkable given the fact that the two brothers had a comparable lifestyle; neither had any comorbidity influencing renal function such as diabetes mellitus, hypertension or cardiovascular disease.

The exact pathogenesis of renal disease in FLD is unknown. Due to the absence of functional LCAT, excess unesterified cholesterol and phospholipid are present in these patients, leading to the formation of lipoprotein X, a protein-free aberrant particle containing FC and PL, associated with glomerular endothelial damage.[9] The composition of typical vacuoles in the glomerular basement of FLD patients has not been fully characterised to date.[9-10] The presence of foam cells in the mesangium of our patient, however, suggests that excess lipid is important in the pathogenesis of the renal damage observed in our FLD patient.

To date no causal treatment for FLD is available. As a consequence, symptomatic treatment encompassing lipid lowering and antihypertensive therapy is commonly started in FLD patients. This combination has been shown to result in decreased proteinuria and stabilisation of pathological sequelae in FLD patients.[11] Beneficial effects of corticosteroid administration have also been described.[12] FLD patients who develop ESRD require haemodialysis or kidney transplantation. Despite evidence of early histomorphological changes consistent with FLD in renal grafts after transplantation, acceptable long-term results have been reported.[13]

Both LCAT gene replacement and enzyme replacement are under development. In a model described by Kuroda and co workers,[14] autologous adipocytes are transfected with human LCAT via a retroviral vector. LCAT secreted by these cells is able to restore enzyme activity in plasma of FLD patients. Recombinant human LCAT (ACP-501)[15] showed excellent results in LCAT knockout mice, rapidly restoring LCAT activity, cholesterol efflux and lipid profiles. rhLCAT is currently being evaluated in FLD patients in a phase I trial.[5]

CONCLUSION

FLD is a recessive lipid disorder ultimately resulting in ESRD. The clinical course of the disease is variable, even in related FLD patients. We demonstrate that apart from glomerulopathy, FLD is also characterised by tubular pathology. Finally, our patients stress the need for LCAT enzyme replacement therapy, which is currently under development in a phase I clinical trial.[5]

ACKNOWLEDGEMENTS

We would like to thank Claartje Koch for her assistance in the family study, and Mahdi Motazacker and Jorge Peter for their assistance in the genetic analysis. G.K. Hovingh and A.G. Holleboom are supported by Veni grants (project numbers 91612122 and 91613031, respectively) from the Netherlands Organisation for Scientific Research (NWO). No conflicts of interest are reported.

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PHOTO QUIZ

Unilateral tongue atrophy and pulmonary malignancy

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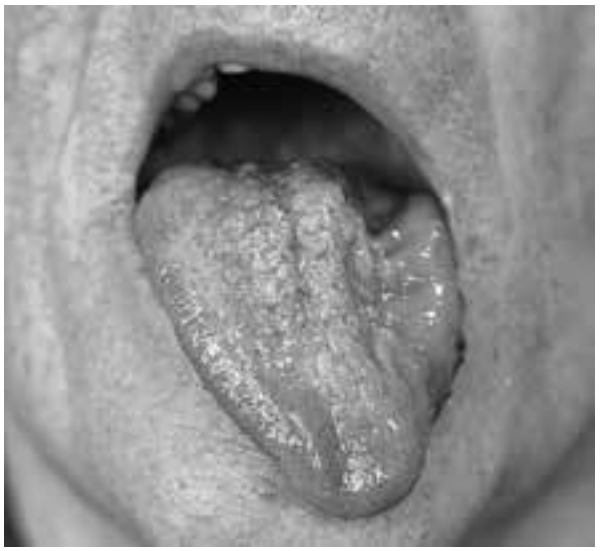
CASE REPORT

An 82-year-old man was referred to the department of pulmonology with a left-sided pneumothorax, which was seen on a chest X-ray requested by his general practitioner. His medical history included a non-small-cell lung carcinoma (NSCLC) T1N0M0 in 2009. With the intention to cure, the patient received radiation therapy for the NSCLC in his left lung. However, a few months later, recurrence of the malignancy in the left lung and metastasis to the right lung was observed on follow-up. The patient and his family did not want any further treatment at that time. In the first year, he progressed relatively well but subsequently, he suffered from progressive weight loss. At presentation, 18 months after the diagnosis of pulmonary metastasis, the patient complained of hoarseness. The chest X-ray showed tumour progression as well as a pneumothorax of the left lung. On physical examination, a remarkable finding was observed (*figure 1*).

Figure 1.



WHAT IS YOUR DIAGNOSIS?

See page 35 for the answer to this photo quiz.

Netherlands
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A patient with cutaneous lesions after liver transplantation

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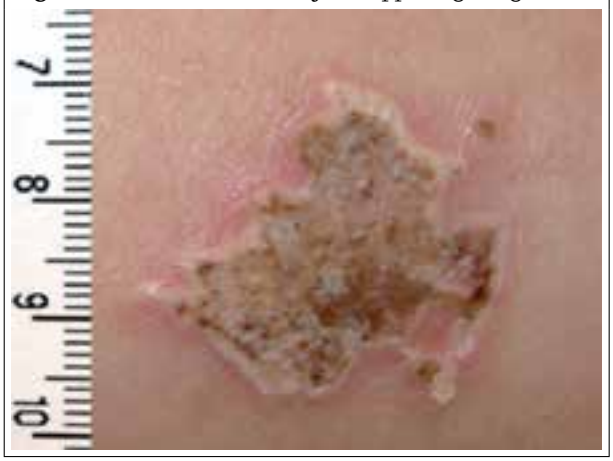
CASE REPORT

A 28-year-old woman was acutely admitted to our hospital because of sudden onset of high fever, chills and abdominal pain. Her past medical history revealed a metabolic disorder complicated by liver cirrhosis, for which she had received a liver transplantation three months earlier. The patient was on immunosuppressants, antiviral medication and *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis. The transplantation was complicated by postoperative bleeding for which coiling of the splenic and gastroduodenal arteries was performed. Antithrombotic prophylaxis consisted of subcutaneous nadroparin. On physical examination at admission, the patient was acutely ill, had high fever, low blood pressure and severe tachycardia. In addition, multiple lesions were seen on the upper legs. The lesions were non-painful, firm and measured up to 2.5 cm in size, with an erythematous, yellow border (*figure 1*). Laboratory investigation revealed: corrected calcium 2.39 (2.20-2.65 mmol/l), phosphate 1.15 (0.80-1.40 mmol/l), creatinine 123 µmol/l (45-90 µmol/l), C-reactive protein 61 mg/l (< 10 mg/l) and leucocyte count 0.9 x 10^9/l (4-11 x 10^9/l). The patient was treated with volume replacement and broad-spectrum antibiotics.

Figure 1. *Cutaneous lesion of the upper right leg*



Over 12 hours her condition stabilised and she gradually recovered. The skin lesions remained unchanged.

WHAT IS YOUR DIAGNOSIS?

See page 36 for the answer to this photo quiz.

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Generalised tonic-clonic seizure and diffuse alveolar haemorrhage

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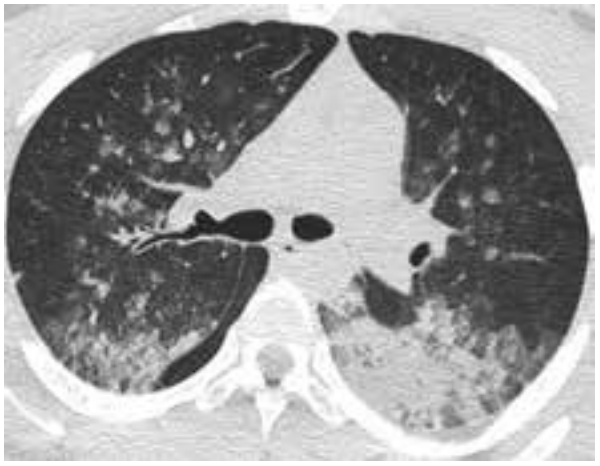
CASE REPORT

A 24-year-old woman was referred to the emergency department for generalised tonic-clonic seizure rapidly controlled with clonazepam. Three months before, the patient had been diagnosed with idiopathic generalised epilepsy and had initially been treated with valproic acid, then levetiracetam with poor compliance. She denied taking any other medications or illicit drugs. Three hours after admission, she presented haemoptysis with an amount evaluated at one glass of blood. Acute respiratory distress rapidly developed, her respiratory rate was 45 breaths/min, and oxygen saturation was 89% on room air. She was transferred to the intensive care unit. Her vital signs were normal except for the respiratory rate, and Sa02 was 98% with oxygen (12 l/min) administered by face mask. Crackles were heard in the lung bases. Physical examination was otherwise unremarkable. Blood cell count showed a decrease in the haemoglobin level from 11.9 g/dl to 10.3 g/dl. Other laboratory tests including serum creatinine level, liver function tests, urinalysis, and coagulation tests were within normal ranges. Electrocardiogram was unremarkable. Thorax CT scan demonstrated declive and perihilar ground-glass opacities (*figure 1*). Lung fibroscopy showed scanty amounts of fresh blood but no endobronchial lesion was found. Bronchoalveolar lavage analysis showed gross bloody fluid. Presumptive treatment of infection combining cefotaxime, rovamycine and cotrimoxazole was given but the bronchoalveolar lavage study failed to detect any pathogens. Search for anti-nuclear, anti-neutrophil cytoplasmic and anti-glomerular basement membrane antibodies was negative. Echocardiogram did not detect heart failure or valvular disease.

Figure 1. *Thorax CT scan showing perihilar and declive ground-glass and infiltrative opacities*



WHAT IS YOUR DIAGNOSIS?

See page 37 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 32)

UNILATERAL TONGUE ATROPHY AND PULMONARY MALIGNANCY

DIAGNOSIS

The history of NSCLC, the hoarseness of voice and unilateral tongue atrophy on physical examination suggested a possible diagnosis of metastasis of the NSCLC with subsequent hypoglossal nerve paresis. This diagnosis was confirmed with magnetic resonance imaging (MRI) of the cerebrum, which showed a tumour of the skull basis suspicious of a bony metastasis of the NSCLC. *Figure 2* displays the MRI with a tumour of 3.4 by 4.1 cm, which shows an infiltration into the hypoglossal canal (*marking*). *Figure 3* shows a t2-MRI with a coronal view of the skull with fatty denervation of the tongue.

Despite this metastasis and the difficulty in swallowing as well as aspiration of food, he did not want any further treatment.

Figure 2. *Canalis hypoglossus and tumour suspect for NSCLC metastasis. MRI t1se after gadolineum*

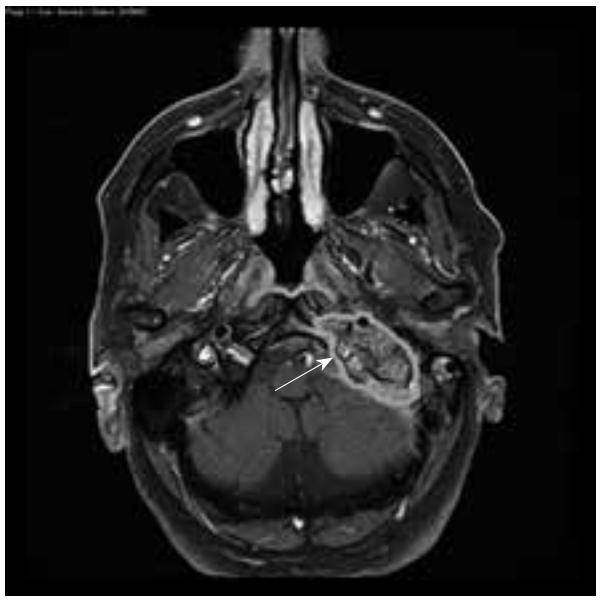
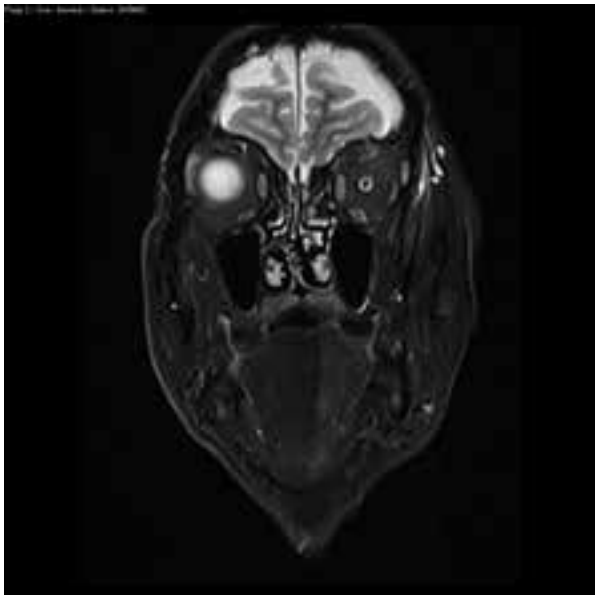


Figure 3. *Fatty tongue denervation. MRI t2cor fat saturation*



ANSWER TO PHOTO QUIZ (PAGE 33)

A PATIENT WITH CUTANEOUS LESIONS AFTER LIVER TRANSPLANTATION

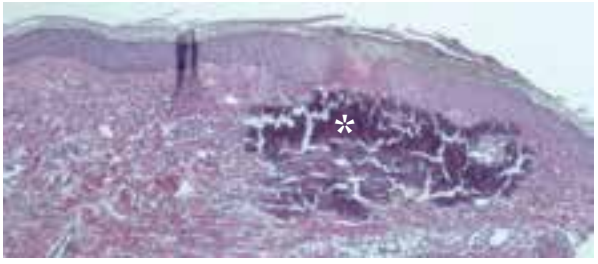
DIAGNOSIS

The diagnosis is calcinosis cutis due to nadroparin injections: a rare non-immunological side effect of an extensively used therapy. The fever was caused by *Staphylococcus aureus* splenic abscess and sepsis. Calcinosis cutis is caused by abnormal cutaneous deposits of calcium and phosphate salts. On physical examination variable presentations can be seen including erythema, blebs, yellow borders, ulcerated plaques and subcutaneous nodules.[1] Histopathological examination showed a dermal deposition of calcium salts (*figure 2*). These calcium deposits cause skin inflammation. Four different types of calcinosis cutis can be identified: dystrophic, metastatic, iatrogenic and idiopathic calcinosis.[2] Dystrophic calcinosis occurs in previously damaged tissue. Metastatic calcinosis develops as a result of hypercalcaemia or hyperphosphataemia caused by renal failure. Iatrogenic calcinosis includes calcinosis due to electromyographic or electroencephalographic electrode components; and after extravasation of intravenously applied calcium gluconate or calcium chloride.[2] The mechanism of calcinosis cutis in the current case is multifactorial. Predisposing factors include high phosphate levels and renal failure around the period of the liver transplantation (metastatic). Precipitating factors include local trauma due to subcutaneous injections (dystrophic), and local elevation of calcium concentrations due to calcium salts contained in nadroparin (iatrogenic).[3] Calcinosis cutis due to, for example, subcutaneous morphine has not been reported until now, suggesting the calcium content of nadroparin plays an essential role in the pathogenesis. The combination of high calcium-phosphate levels including local deposition of calcium leads to an accumulation of the solubility product at the injection site.

Calcinosis cutis is a rare adverse reaction; however, because it is poorly recognised, the condition might be under-diagnosed. Treatment includes discontinuation of nadroparin. Generally, spontaneous recovery occurs in several weeks to months. In high-risk patients, such as in those with renal failure, the use of dalteparin, a non-calcium containing low-molecular-weight heparin, is advised.

Conclusion: calcinosis cutis due to calcium-containing low molecular weight heparin.

Figure 2. *Calcinosis cutis: dermal deposition of calcium salts (*), recognisable by the intense basophilic staining. Haematoxilin-eosin staining (x10)*



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ANSWER TO PHOTO QUIZ (PAGE 34)

GENERALISED TONIC-CLONIC SEIZURE AND DIFFUSE ALVEOLAR HAEMORRHAGE

DIAGNOSIS

A diagnosis of diffuse alveolar haemorrhage (DHA) related to generalised tonic-clonic seizure was made.

DISCUSSION

Diagnosis of DHA was based on the temporal relationship between the onset of seizure and haemoptysis, and the negative investigations. The patient recovered totally within 72 hours with oxygen therapy. Thorax CT scan was unremarkable one month later.

DHA, suggested by the association of haemoptysis, new pulmonary infiltrates on thorax CT scan and anaemia, results from diffuse bleeding into the acinar portion of the lungs.[1] An early diagnosis of the underlying disease – including immune causes (mainly small-vessel vasculitis, anti-glomerular basement membrane antibody disease, connective tissue disease) and non-immune causes (infections, congestive heart failure, barotraumas and clotting disorders) – as well as an appropriate treatment are mandatory.[1] Generalised tonic-clonic seizure is a rare cause of DHA.[2,3] Two main mechanisms are advocated. First, neurogenic pulmonary oedema – observed in central nervous system disorders – via an inappropriate autonomic nervous system reaction is associated with an increase in pulmonary capillary hydrostatic pressure and capillary permeability, resulting in alveolar leakage of fluid and alveolar haemorrhage.[2,3] Second, the capillary pressure significantly increases at the time of tonic-clonic seizure, leading to structural alteration of the alveolar septal barrier, and secondary pulmonary haemorrhage and haemoptysis, as observed during severe exercise.[2,3] Spontaneous resolution of DHA secondary to generalised seizures is usually observed under supportive treatment with oxygen and mechanical ventilation if necessary, but positive end-expiratory pressure should be avoided since it may worsen intracranial hypertension.[2,3] Finally, recurrence of DHA is possible after further episodes of generalised tonic-clonic seizure as observed in our patient who had three similar episodes during the two following years related to poor compliance to levetiracetam treatment.[2]

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SPECIAL ARTICLE

Evaluation of the threshold value for the Early Warning Score on general wards

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ABSTRACT

Introduction: The Early Warning Score (EWS) is used for early detection of deteriorating vital parameters and has been correlated with adverse outcomes. Unfortunately, neither its value on general wards nor the optimal cut-off value have been investigated. We aimed to find the optimal cut-off value for EWS on general wards, and investigated the possibility to raise this value from EWS ≥ 3 without compromising sensitivity too much.

Methods: From May 2010 until May 2011, EWS was calculated from vital parameters in all patients in medical and surgical wards in the Medical Centre Alkmaar. Cut-off value was defined as EWS ≥ 3, unless otherwise specified. Six responses were defined and categorised as interventions (infusion prescription, medication changes, ICU consultation) and other actions (no action, change EWS cut-off value, oxygen supplementation), and it was registered whenever the threshold was exceeded.

Results: 71,911 EWS values were obtained, 31,728 (44%) on medical wards and 40,183 (56%) on surgical wards. On medical wards, the cut-off value was exceeded 3734 times, and response was registered in 29% of the cases with 141 (12%) interventions. On surgical wards, the cut-off value was exceeded 3279 times, and response was registered in 19% of the cases with 633 (36%) interventions.

Sensitivity and specificity for EWS ≥ 3 could not be calculated. For a calculated cut-off at EWS ≥ 4, sensitivity decreased to 74%.

Conclusion: Raising the EWS threshold to 4 on general wards in the hospital would lead to an unacceptable decrease in sensitivity. Therefore, we recommend that the pre-defined cut-off should remain 3, with the possibility to personalise the threshold.

KEYWORDS

Early warning score, general ward, threshold value, vital signs

INTRODUCTION

Physiological deterioration is recognised rather late on general wards.[1] This is one of the reasons that patients arriving at an intensive care unit (ICU) from general wards have lower survival rates than patients admitted from operation theatres or emergency rooms.[2] Early recognition of critically ill patients can improve patient safety and may even lower hospital mortality.[3] In order to identify the critically ill, many scoring systems have been developed.[4,5] Most of these scores use periodic observation of physical signs, including vital signs, carried out by nursing staff. These parameters are used to calculate a score, and a response is required if the predefined threshold is exceeded. Different scores, thresholds and responses have been evaluated for emergency and high care units, but none of these systems have been validated for use on general wards. Nonetheless, many hospitals have embraced these scores for their wards, especially when introducing an ICU outreach team or medical emergency team. Previously, a high Early Warning Score (EWS) was correlated with adverse outcomes, although results from different studies are inconsistent.[6] In addition, research was focused on newly admitted patients. We intended to relate EWS on hospital wards to mortality. The threshold value used for EWS is usually 3. It is unclear whether this cut-off value is applicable for general wards, since high sensitivity is accompanied by many false-positive phone calls to the physician.

We aimed to find the optimal threshold value for EWS on a general ward, and investigated whether it was possible to raise this value from 3 without compromising sensitivity too badly.

METHODS

We investigated the possibility to raise the standard cut-off value for the EWS score from 3 to 4 or 5. Required sensitivity was defined at 90%. This implies that 90% of

all interventions would take place at EWS values equal to or exceeding the predefined cut-off. A power analysis revealed that at least 140 registered interventions were needed in order to confirm 90% sensitivity with a 95% confidence interval of 10% (85-95%).

From 1 May 2010 to 20 May 2011, nursing staff recorded vital parameters at least twice a day in all patients on three medical and two surgical wards in the Medical Centre Alkmaar. Medical Centre Alkmaar is a teaching hospital with about 700 beds (Jaardocument Stichting Medisch Centrum Alkmaar 2010) and 14 ICU beds. EWS values were calculated automatically from these parameters once the vital signs were entered into an electronic patient record (McKesson Horizon version 2.08.08.01) (*table 1*).

If the calculated EWS value exceeded the cut-off value, usually 3, the program rendered a signal to contact the physician. In addition, a two-point raise in EWS between two consecutive observations, possibly indicating deterioration of a patient's condition, was reported by the computer program. In these cases a physician was always contacted. Based on previous EWS scores and after physical examination, an individual cut-off value could be set in order to lower the number of phone calls to the physician.

Whenever a physician was contacted, the relevant following action (response) was registered. We defined six different responses: no action, change EWS cut-off, oxygen supplementation, infusion prescription, change in medication, and ICU consultation. These responses were grouped into interventions (infusion prescription, change in medication and ICU consultation) and other responses.

Sensitivity for a cut-off EWS=X was calculated by the following formula:

(*interventions* for EWS ≥ X/total interventions)*100%

This was repeated for the different EWS values, to calculate sensitivity for possible cut-off values.

Specificity was calculated by the formula:

(*other responses* for EWS < X/total other responses)*100%

This was also repeated for the different EWS values.

In addition, we compared in-hospital mortality for all patients admitted to the forenamed wards in the study period for their maximum EWS values (EWS_{max}). We did the same for one-year overall mortality and one-year overall mortality with exclusion of hospital mortality. The hospital database depends on people in the community, for example family members and general practitioners, to report the deaths outside the hospital. Therefore, these data are probably incomplete.

RESULTS

In a period of almost 13 months (May 2010-May 2011), 71,911 EWS values were registered on the participating wards in the Medical Centre Alkmaar. A little more than half (56%, 40,183) were registered on surgical wards, 44% (31,728) on medical wards. All patients admitted in the aforementioned period were included and EWS was calculated at least twice daily.

EWS values were distributed differently on the two wards. Mean EWS values are higher on medical wards (1.4) than they are on surgical wards (1.2) (*figure 1*). The cut-off value was reached in 12% (3734) of EWS values registered on medical wards, as opposed to 8% (3279) of all cases on surgical wards.

The pre-defined cut-off value to contact the physician was EWS ≥ 3, or an increase of more than two points between two consecutive measurements. EWS cut-off could also be set otherwise by the physician. Whenever an EWS value higher than the cut-off value was registered, a response was recorded. The six different responses defined were no action, change EWS cut-off, oxygen supplementation, infusion prescription, change in medication, and ICU consultation.

Responses were registered on medical wards in 29% of the cases with EWS exceeding threshold. Interventions, predefined as the responses infusion prescription, change in medication and ICU consultation, were observed 141 times (12%). On surgical wards, 19% (633) of all responses were registered. The percentage of interventions was 36 (225), much higher than on medical wards. In addition,

Table 1. *Early Warning Score scoring system*

EWS	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Pulse rate				51-100	101-110	111-130	>130
BP (systolic)	<70	70-80	81-100	101-200		>200	
Respiratory rate		<9		9-14	15-20	21-30	>30
Temperature		<35.1	35.1-36.5	36.6-37.5	>37.5		
Consciousness				A	V	P	U

EWS = Early Warning Score; BP = blood pressure; A= alert; V=responsive to voice; P=responsive to pain; U=unresponsive. Worried about patient's condition: 1 point; Urine production below 75 ml during previous 4 hours: 1 point; Saturation below 90% despite adequate oxygen therapy: 3 points.

Figure 1. *Distribution of EWS with or without exceeding threshold on different wards on: A) Medical wards; B) Surgical wards*

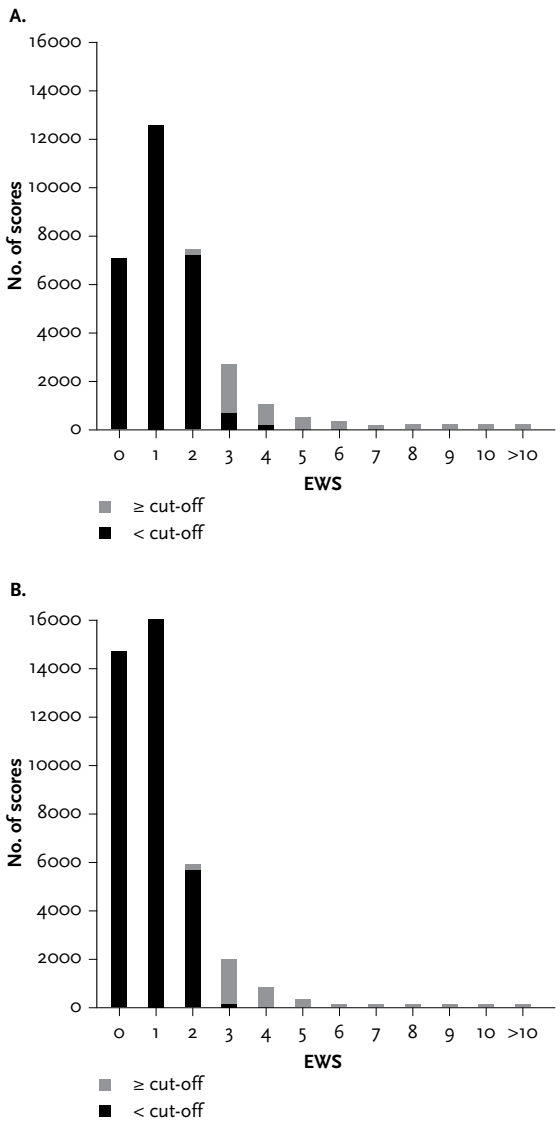
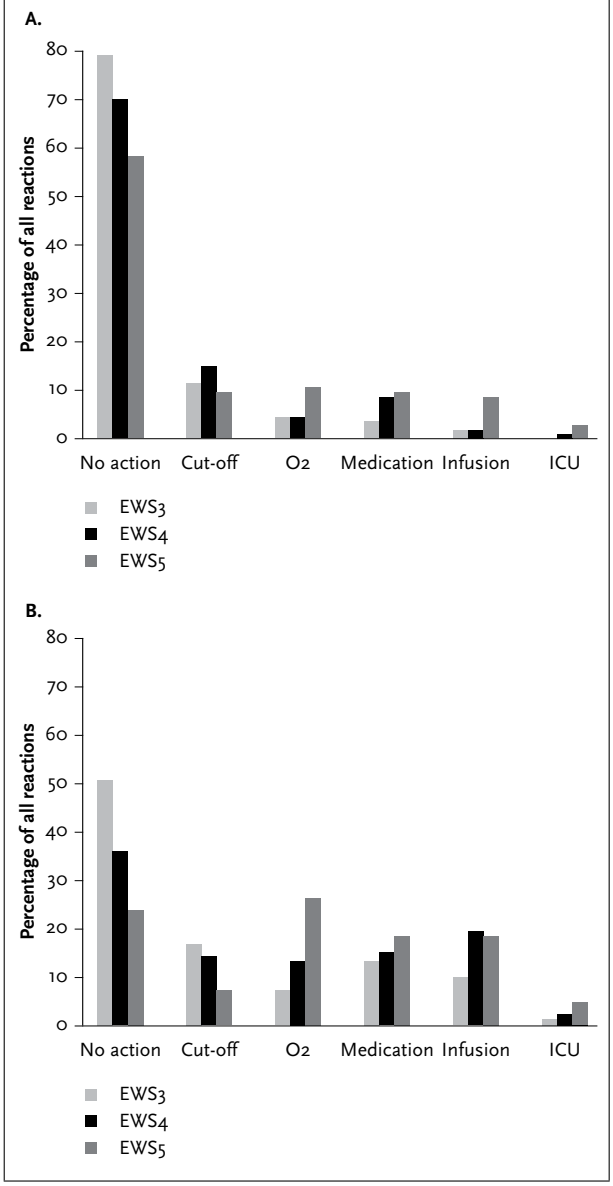


Figure 2. *Reactions registered for different EWS values on: A) Medical wards; B) Surgical wards*



the other responses were also distributed differently on the different ward types (*figure 2*). For example at EWS 3, the response no action was found in 51% on surgical wards, as opposed to 79% on medical wards. Overall, the higher the EWS, the more changes in oxygen, medication and infusion regime as well as ICU consultations were seen. The number of no action and change EWS responses decreased with increasing EWS. This effect was seen on all wards.

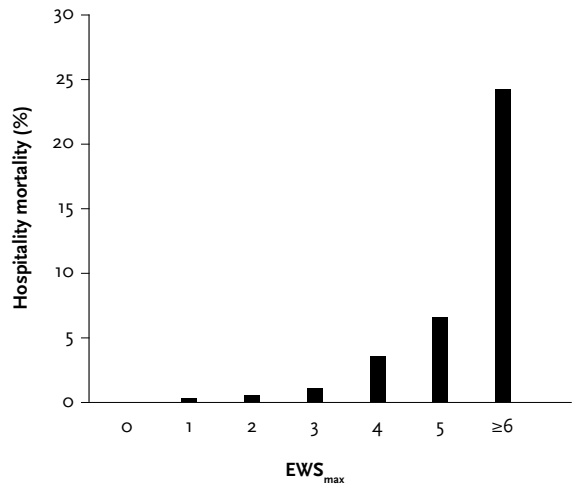
Sensitivity was calculated from the total number of responses and the number of interventions. We required 90% sensitivity with a 95% confidence interval of 10%. By dividing the number of interventions for EWS ≥ X by the total number of interventions, sensitivity was calculated for cut-off EWS=X. The EWS system was introduced in our hospital with the cut-off X=3. Therefore, all registered responses, thus all interventions, were found at EWS ≥ 3. As a result, it was not possible to calculate sensitivity and specificity for cut-off EWS ≥ 3 correctly, since sensitivity would be 100% and specificity 0%. Raising the cut-off value (X) decreased sensitivity and increased specificity. Both sensitivity and specificity found for any X was higher on medical than on surgical wards as can be seen in *table 2*. For cut-off at EWS ≥ 4 (X=4), sensitivity was 79% on medical wards and 71% on surgical wards. Specificity was 51% on medical and 49% on surgical wards. Overall, sensitivity was 74% and specificity 51% for X=4.

Table 2. *Sensitivity and specificity for different Early Warning Score values*

	EWS	3	4	5
Sensitivity	Medical	x	79%	60%
	Surgical	x	71%	46%
	Total	x	74%	52%
Specificity	Medical	x	51%	74%
	Surgical	x	49%	72%
	Total	x	51%	73%

When X=5 was used, overall sensitivity was 52%, 60% on medical and 46% on surgical wards. Specificity was 73%, with hardly any difference between medical and surgical wards (74% *vs* 72%). Overall, 74% of all interventions took place at EWS ≥ 4, which is less than the 90% we aimed for. To analyse mortality, the deaths for EWS_{max} 6 and higher values were clustered to give a reliable number, due to a relatively small number of values for $EWS_{max} \geq 6$. Hospital mortality was 0% for $EWS_{max}=0$ and increased almost logarithmically to 1% for EWS=3 and 24% for $EWS_{max} \geq 6$ (*figure 3*). One-year overall mortality and one-year mortality excluding hospital mortality also increased for higher EWS_{max} values, although differences were somewhat less. One-year overall mortality was 3%, 12% and 40% for $EWS_{max}=0$, $EWS_{max}=3$ and $EWS_{max} \geq 6$ respectively; when hospital mortality was excluded this was 3%, 11% and 16% for the respective EWS values.

Figure 3. *Hospital mortality versus maximum EWS during hospital stay*



DISCUSSION

Although high EWS has been correlated with adverse outcomes, an optimal threshold value for EWS on general wards has not been established previously.[5] The system was introduced in our hospital using 3 as a cut-off value, since this cut-off is usually applied in other settings. Thus, it was not possible to calculate sensitivity or specificity for a threshold at 3, while 3 was the independent variable. For a cut-off value raised to EWS ≥ 4, the calculated sensitivity was 74%, far below the predefined 90%. Sensitivity decreased even further to 52% if EWS ≥ 5 was used. Thus, raising EWS cut-off for all patients would lead to an unacceptable decrease in sensitivity. Since sensitivity for EWS ≥ 3 could not be calculated and sensitivity for EWS ≥ 4 was inadequate, we presume that 3 is the optimal cut-off value.

By ensuring high sensitivity, specificity is often compromised. A lower threshold results in increased workload, at the risk of making staff less cautious.[5] In particular on medical wards, where mean EWS is higher, an unadjusted cut-off at 3 means 12 phone calls to the physician a day. Although several of these patients may benefit from the attention generated by this extra trigger, most certainly not all these patients are critically ill. Therefore, we included the option to change the EWS cut-off point, based on previous recordings and actual physical state. This will increase both the sensitivity and specificity of the EWS system. However, the majority of patients will not have a personalised threshold and a general cut-off must be used for their EWS values. Another exception to the standard threshold is an increase of two points or more between two consecutive measurements, which could mean rapid deterioration and should always prompt action.

Our results show that EWS is a good predictor for mortality, in-hospital mortality as well as one-year mortality. We could therefore conclude that EWS adequately identifies critically ill patients.

Since the system for registering out-of-hospital mortality depends on others to report death, this registration is probably incomplete. Since reporting is probably approximately equal for all EWS_{max} groups, it is unlikely that this affects the distribution between the different EWS_{max} values.

In previous studies, EWS and similar systems have been used on emergency wards, and for new admissions, but no trigger system has been validated for general wards.[6] However, the emergence of ICU outreach teams has prompted the implementation of these systems to identify patients at risk.[7] Reviews describing the use of many track and trigger systems in various countries state that many

systems have an unacceptably low sensitivity, and that none of the systems identifies the critically ill very well.[4,8] In addition, differences in discriminatory power between the systems may be accounted for by differing thresholds.[5] Nurses trained in EWS performed a little better in identifying a deteriorating patient, although, oddly enough, they hardly ever used EWS.[9] A systematic review found inconclusive evidence regarding the effectiveness of EWS and intensive care outreach teams.[10] Moreover, when compared with an ICU outreach team, a team composed of the patients usual care providers achieved similar results in reducing unexpected mortality, but not overall mortality.[12,13] Despite all these uncertainties, the introduction of early warning systems in the United Kingdom coincided with a decrease in mortality and cardiac arrest rate.[11] Currently, a multicentre study in the Netherlands is evaluating the effectiveness and the cost-effectiveness of rapid response teams (COMET study).

The strength of this study is its large number of patients and EWS values. By including three medical and two surgical units a representative case-mix for general wards was created, and differences between these types of wards could be observed. In general, patients on medical wards were found to have higher EWS values than patients on surgical wards. In addition, results suggest that the same EWS value on different wards does not appear to have the same predictive value. A change in therapy at EWS=3 was recorded on surgical wards in 32% of cases, as opposed to 10% on medical wards.
This could be explained by the fact that the average patient on a surgical ward is younger, has less extensive comorbidity and faces different problems. It was suggested earlier that different triggers could be appropriate for medical and surgical patients.[14] The individual adjusted EWS takes care of some, but not all of these problems.
Although it was a single-centre study, results can probably be generalised for similar hospitals, due to the large number of patients, the different wards and the time course. However, hospitals with different patient categories, such as university hospitals, would need to be studied separately.

A limitation of this study is that only a minority of the relevant following actions are registered. In almost three-quarters of all EWS scores exceeding threshold, no response was reported. Medical wards did a little better than surgical wards, with 29% *vs* 19%. This difference may be another explanation for the different responses for EWS=3. We do not know whether one category or all categories of responses where underreported. Underreporting of ICU consultations was made unlikely by comparing ICU admissions in one month to the EWS data (data not shown).
It is very well possible that many no action situations have gone by without listing. Since it is reasonable to assume that no action responses would have been registered mostly for lower EWS values, more registration would increase specificity. We presume that better registration of no action responses as well as more frequent use of personalised thresholds adds to a higher sensitivity and specificity on medical wards, compared with surgical wards. Sensitivity is not influenced by underreporting of a no action response.
In addition, due to the way our data were collected, we could only analyse EWS values per ward, rather than per patient. Therefore, it is very well possible that EWS values were more frequently registered in the most severely ill patients, causing a relative overestimation of high EWS values. An explanation for the low number of interventions we found could be that many registrations led to only one intervention. However, this would only influence specificity, not sensitivity. It would be interesting to analyse the frequency of EWS registrations, because an increase in frequency without an increase in the number of interventions could also imply that it is useless to measure the EWS more often.

CONCLUSION

Raising the EWS threshold to 4 on general wards in the hospital would lead to an unacceptable decrease in sensitivity. Therefore, we recommend that the pre-defined cut-off should remain at 3, with the possibility to personalise the threshold.

ACKNOWLEDGEMENTS

T. van der Ploeg gave statistical advice. A. Torrisi created the computer system to obtain the responses. N. Ket-Groeneveld supplied the mortality numbers.

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Netherlands
The Journal of Medicine

SPECIAL ARTICLE

Registering complications at admission via the emergency department: an opportunity for improvement

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ABSTRACT

Background: To monitor and improve the quality of care we provide it is important to register complications. Complications occurring after discharge or after treatment at outpatient clinics are usually not registered and complications occurring in domains other than where they originated may be missed. The emergency department (ED) may offer an opportunity to register these complications. This study assesses the prevalence and nature of complications in patients at the moment of acute admission by internists.

Methods: A retrospective cohort study over a five-month period was performed in which we reviewed the charts of all patients who were admitted to our hospital via the ED by internists. We investigated the number, nature, preventability and severity of complications present at the moment of admission.

Results: In total, there were 1128 admissions. Of these, 284 patients were admitted 324 times (28.7%) due to a complication. The most common complication was medication-related (43.5%), in particular bleeding while using anticoagulants. The second most prevalent complication was chemotherapy-related (26.9%), while 17.3% were due to a procedure. Up to 27.8% of all complications were considered preventable. Eighteen (6.3%) patients died during their admission, seven (2.5%) did not recover completely. A total of 23.1% of all complications originated in specialities other than internal medicine.

Conclusion: Complications are a major reason for hospitalisation. Registering complications present at admission gives broad insight into the complications following the care doctors provide. It is important to understand these complications better to prevent such admissions.

KEYWORDS

Adverse drug events, adverse drug reaction, adverse event, complications, internal medicine

INTRODUCTION

Complications, including adverse drug reactions (ADRs), are common but definitely not harmless. In a way these complications mirror our quality of care. It is therefore important to register these complications to monitor and improve the quality of care we provide. In certain disciplines, such as surgery, it has been common practice for years to register complications,[1,2] but in internal medicine we are just starting and lack extensive experience. To our knowledge, complications occurring after discharge or after treatment in outpatient clinics are not registered. Furthermore, it is our experience that many specialists do not treat their own complications. Hence, important feedback to prevent further complications will not always be reported to the specialist where the complication originated.

Until recently, most studies concerning complications focussed on complications during hospitalisation[3-9] and ADRs causing admission.[10-15] To our knowledge, the number of admissions due to complications that are not ADRs has not been studied. The emergency department (ED) can offer an opportunity to register all kinds of complications originating in more than one stage of treatment and in more than one speciality.

The present study aims to assess the prevalence and nature of complications in patients at the moment of acute admission by internists in a Dutch university medical care centre.

METHODS

Our study was conducted in a secondary and tertiary university medical care centre (Maastricht University Medical Centre; MUMC) in the Netherlands. All patients with an acute, non-planned admission via the ED by internists during the period May-September 2010 were included in the study (n = 1128). Most of our patients are referred by a general practitioner, except for some high urgency (ambulance) patients and some self-presenters. Outside office hours, a general practitioner assesses these self-presenters in a location adjacent to our ED. During office hours, acute internists assess both referred and non-referred patients at the ED and decide on further treatment, including admission to the hospital. In our hospital, acute internists assess patients with general medical problems as well as oncological, haematological, nephrological, gastrointestinal and rheumatological problems.

Retrospectively, we reviewed all admission charts. From these charts, we retrieved information on whether complications were present at the moment of admission and whether these complications led to hospitalisation. In addition, we evaluated the discharge letter. A complication was defined, according to the Dutch Internal Medicine Association,[16] as 'any event or state during or following treatment by a specialist that influenced the health of the patient in such way that renewed treatment was necessary or that it led to damage'. All investigators successfully completed an E-learning course about the registration of complications.[16]

All complications were registered following national guidelines,[16] hereby not only registering the complication itself but also its severity (with external factors and procedures that were necessary to diagnose or treat the complication taken into account). If a patient was admitted due to more than one complication, the main complication was scored. We registered the nature of all complications: medication-related, chemotherapy-related, diabetes mellitus-related, procedure-related, or others and we registered which speciality caused the complication. Two investigators independently evaluated whether the complication was preventable or not. In case of disagreement a third investigator decided on this issue. To determine the severity of a complication, all complications were categorised as a complication with (a) full recovery, (b) permanent damage or (c) leading to death. Moreover, we evaluated the survival *during* hospitalisation.

SPSS Statistics version 18 (SPSS Inc, Chicago, Illinois) was used to make Kaplan-Meier survival curves after a follow-up of one month. A log-rank (Mantel-Cox) test was used to compare the survival distributions per type of complication, sex and six age groups (<40 years; 40-50 years; 50-60 years; 60-70 years; 70-80 years; >80 years). To calculate the interobserver agreement we used Cohen's kappa.

The Medical Ethics Committee of the institution approved this study.

RESULTS

In the period May-September 2010, there were 3289 admissions in our hospital via the ED of whom 1128 were admitted to the internal medicine department (*table 1*). In total, 284 patients were admitted 324 (28.7%) times due to a complication. The median age was 66 years.

Complications

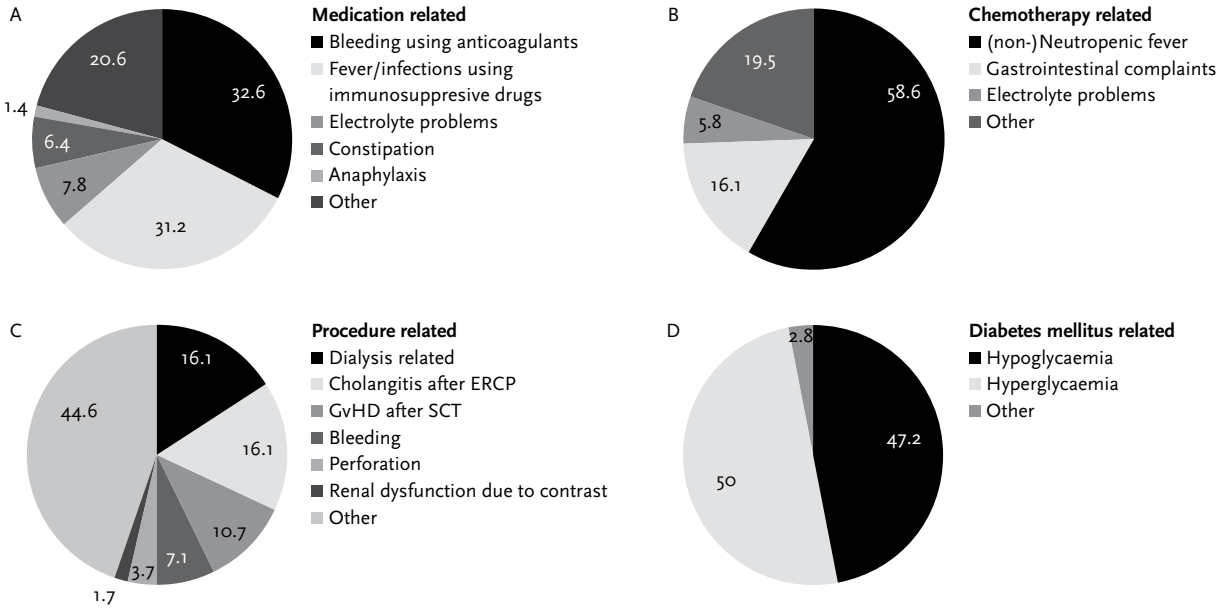
The most common complication was medication-related (43.5%), with bleeding while using anticoagulants (32.6%; 14.2% of total) as most prevalent in this category (*table 1* and *figure 1*). Another 44 (31.2%; 13.6% of total) medication-related complications were fever or an infection while using immunosuppressive drugs. The second most common group of complications was chemotherapy-related (26.9%). Fifty-six patients (17.3%) were admitted because of complications following a procedure. Thirty-six (11.1%)

Table 1. *Patient characteristics and their complications*

Study population	**n (%)**
Admissions for internal medicine	1128 (100)
Admissions because of complications	324 (28.7)
Patients admitted because of complications	284 (25.2)
Sex, female	160 (49.4)
Median age in years (range)	66 (21-96)
Duration of admission:	
Days (median, range)	8 (1-92)
Missing information	16 (4.9)
Complications	**n (%)**
Medication-related	*141 (43.5)*
Bleeding using anticoagulants	46 (14.2)
Coumarins	19 (5.9)
Other anticoagulants	27 (8.3)
Fever/infections using immunosuppressive drugs	44 (13.6)
Electrolyte problems	11 (3.4)
Constipation	9 (2.8)
Anaphylaxis	2 (0.6)
Other	29 (9.0)
Chemotherapy-related	*87 (26.9)*
Non-neutropenic fever	34 (10.5)
Neutropenic fever	17 (5.2)
Gastrointestinal complaints	14 (4.3)
Electrolyte problems	5 (1.5)
Other	17 (5.2)
Procedure-related	*56 (17.3)*
Dialysis related	9 (2.8)
Cholangitis after ERCP	8 (2.5)
GvHD after SCT	6 (1.9)
Bleeding	4 (1.2)
Perforation	2 (0.6)
Renal dysfunction due to contrast	1 (0.3)
Other	26 (8.0)
Diabetes mellitus-related	*36 (11.1)*
Hypoglycaemia	17 (5.2)
Hyperglycaemia	18 (5.6)
Ketoacidosis	2 (0.6)
Other (renal dysfunction)	1 (0.3)
Other	*4 (1.2)*
While on a waiting list	*3 (0.9)*

ERCP = endoscopic retrograde cholangiopancreatography; GvHD = graft versus host disease; SCT = stem cell transplantation.

Figure 1. *Numbers are percentages of; A) medication-related complications, B) chemotherapy-related complications, C) procedure-related complications, and D) diabetes mellitus-related complications*



ERCP = endoscopic retrograde cholangiopancreatography; GvHD = graft versus host disease; SCT = stem cell transplantation.

patients were admitted with diabetes mellitus-related complications. Overall, infections and fever secondary to immunosuppressive drugs or chemotherapy were the most prevalent complications (95; 29.3%). In 4% (n=13) of the admissions more than one complication was present.

Figure 1 illustrates the complications per category in more detail. In the medication-related category, anticoagulants and immunosuppressive drugs were the main causes of complications. Fever was the most prevalent chemotherapy-related complication.
Dialysis-related problems and cholangitis after endoscopic retrograde cholangiopancreatography (ERCP) accounted for 32.2% of the admissions in the procedure-related category.

Severity of the complications
The median duration of hospital stay was eight days in our cohort. While most (92.3%) of the patients recovered completely, 18 (6.3%) patients died (*figure 2*), and in seven patients the complication led to irreversible damage.
Figure 2 shows the survival of the whole cohort, with an overall 28-day survival of 93.7% (*figure 2A*). There were no statistically significant differences in survival for sex (p=0.53) (data not shown), for each type of complication (p=0.62) (*figure 2B*) nor for the different age groups (p=0.52) (data not shown).

Preventability of complications
Up to 27.8% of the complications were considered preventable (*figure 3*). The authors reached consensus on the preventability in 95% with a high inter-observer agreement (κ = 0.89). Nearly all chemotherapy-related complications were judged inevitable, whereas most of the diabetes mellitus-related complications were judged preventable (69.4%). Of the patients with the complication 'bleeding while using coumarins', 63.2% had an international normalised ratio (INR) higher than 3. This bleeding was therefore judged preventable.

Domains in which complications originated
Most of the complications we found were related to treatment provided by internists (76.9%). Haematological and oncological treatments were responsible for half of the complications (49.4%) (*table 2*).
Other specialists than internists contributed to 23.1% of all admissions, mainly cardiology (13.9% of total). The majority of these complications were gastrointestinal bleeding while being treated with anticoagulants for atrial fibrillation.

DISCUSSION

Complications are a major reason for admissions via the ED by internists. In our study, complications were the reason for hospitalisation in 28.7% of all emergency admissions by internists. To our knowledge, data on the frequency and preventability of admissions by internists due to a complication have not been studied before in the Netherlands or elsewhere.

Figure 2. *Survival during hospitalisation*

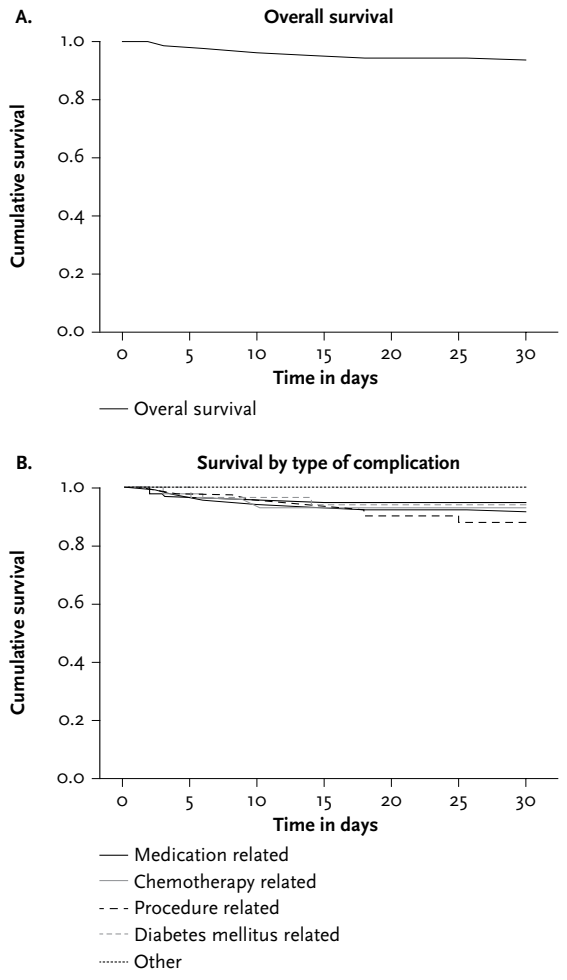


Table 2. *Domains in which complications originated*

Internal medicine	**n (%)***
Oncology	70 (21.6)
Haematology	53 (16.4)
Endocrinology	41 (12.7)
Nephrology	35 (10.8)
Gastroenterology	30 (9.3)
Immunology	7 (2.2)
Other internal medicine	13 (4.0)
Total	249 (76.9)
Other domains	**n (%)***
Cardiology	45 (13.9)
General practitioner	9 (2.8)
Surgery	7 (2.2)
Neurology	4 (1.2)
Psychiatry	4 (1.2)
Urology	2 (0.6)
Rheumatology	2 (0.6)
Other	2 (0.6)
Total	75 (23.1)

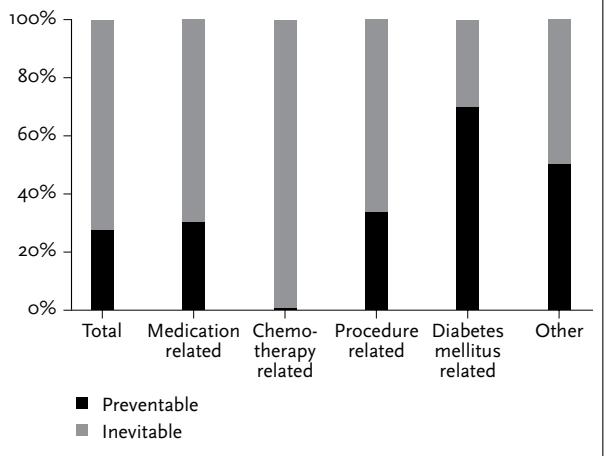
***Percentages are of total (n=324).**

Worldwide, the incidence of complications *during* hospital stay is substantial.[3-9] For example, in Canada a complication rate of 7.5% was found,[7] compared with 5.7-12.3% in Europe[3-6,8] and 4.5% in Colombia.[9] In the Netherlands, a retrospective patient record review study showed that the national incidence of complications among hospitalised patients was 5.7%, of which 39.6% were judged preventable.[3] Focussing on the internal medicine department, a complication rate of 5.4% was found, of which 25.7% were judged preventable. In our study, the incidence of complications was much higher, but the percentage of complications that were judged preventable was comparable (27.8% and 25.7%, respectively). The higher incidence we found could be explained by the fact that the aforementioned studies assessed complications occurring *during* hospitalisation in all hospitalised patients, including electively admitted patients, whereas our study focussed on *the moment of acute admission* only. Comparing the prevalence of complications occurring in electively admitted patients with the complication rate of patients presenting to the ED with complaints that turn out to be a complication of earlier provided treatment, is difficult.

Although little is known about the prevalence and nature of complications at the time of admission, some studies have investigated the rate of medication-related admissions.[10-15] Two German studies found an adverse drug reaction (ADR) related admission rate of 0.92-2.4%,[12,13] one French study found an admission rate of 3.19%,[14] and a Slovenian study of 5.8%.[15] In the Netherlands, a multicentre study (Hospital Admissions Related to Medication; HARM study) showed that 5.6% of the unplanned admissions were possibly or probably medication-related.[10] In our study, we found a higher medication-related admission rate of 12.5%. However, our study focussed on admissions by internists, while the aforementioned studies evaluated ADR hospital admissions by all specialists. Polypharmacy is common in patients treated by internists,[17] which leads to a higher risk of medication-related admissions. This might explain the difference in prevalence.

The HARM study, like our study, found that most (20.2%) of the medication-related admissions were caused by medications that affect blood coagulation (antiplatelet drugs (8.7%), oral anticoagulants (6.3%), non-steroidal anti-inflammatory drugs (NSAIDs (5.1%)). This was also found in other studies.[11,13,15] The most important adverse event of anticoagulants, which reduce the risk of thromboembolism very effectively, is bleeding. Periprocedural reversal and bridging of these agents has recently been reviewed in this journal.[18] Antidiabetic drugs accounted for 11.1% of the admissions in our study, which is comparable to the HARM study (12.3%).

Figure 3. *Preventability of the different types of complications*



Most complications found in our study were mild, although they did lead to hospitalisation, and most patients recovered completely, which is comparable with previously discussed studies.[3-5,7-11,13,14] We found a mortality rate of 6.3% of patients admitted due to a complication, which is comparable with the mortality rates found in studies investigating ADR-related admissions (1.7%-6.3%)[10,11,13] and studies investigating complications *during* hospital admissions (3%-8%).[4-6,9]

Nearly 30% of the complications were judged preventable, of which the diabetes-related complications were most often judged preventable (69.4%). The latter is a consequence of the fact that we judged a hyperglycaemia due to, for example, non-compliance as preventable. This is open for debate, as it is extremely difficult to regulate diabetes strictly within the limits of hyperglycaemia and hypoglycaemia.

The oncologist and haematologist accounted for most of the admissions due to a complication (21.6%). Most of these complications were infections or fever shortly after chemotherapy. Interestingly, 23.1% of the complications were caused by other specialities than internists, in particular the cardiologists (13.9%). However, we did not investigate admissions by, for example, cardiologists due to a complication following treatment started by internists. It is to be expected that other specialities treat complications caused by internists as well. This demonstrates that effective feedback between the different specialities is of utmost importance.

Complications (and their treatment) are not only potentially dangerous, but also expensive. A study performed in Germany found that ADRs account for €400 million per year,[13] while in the United Kingdom the extra bed-days alone would account for £1 billion a year.[6] The total direct medical costs associated with complications in the Netherlands was found to be 2.4% of the national health care budget (total €14.5 billion in 2004), with preventable complications accounting for 1.1%.[19] This emphasises that prevention of complications is relevant for the society as a whole, which stresses the need to get more insight into these (preventable) complications. In our study 27.8% of all complications were judged preventable.

Although complications should be avoided as much as possible, they will continue to occur. Therefore, complications challenge us to continually evaluate our own practice and its organisation. As registration and analysis of adverse outcomes are strong indicators of quality,[2] registration and analysis *per se* may improve our care. A reliable and constructive way to provide feedback on these complications should also be designed.

Limitations of the study

Our study has some limitations. Firstly, it is a small study based on one department, the internal medicine department, of one university hospital. It is important to emphasise that we did not study all the complications that occurred, since we focussed on emergency admissions by internists. We therefore could not include complications caused by internists that were treated by other specialities. To solve this problem, all admissions for all specialities should be included. Secondly, our study included patients who are admitted by internists via the ED only. Therefore, the results cannot be extrapolated to other settings. Thirdly, we did not investigate how many patients experienced a complication in relation to the number of treatments provided since this was not the aim of the study. Hence, it is important to read this study in the right perspective. Fourth, our study cannot be extrapolated to other countries without correcting for differences in the organisation of the health care system. This study, despite its limitations, does provide insight into the prevalence of complications at the moment of admission and justifies a more extensive study, which includes patients of more specialities.

Furthermore, hindsight bias might have occurred, as it is a general weakness of retrospective studies.[20] Knowing the outcome of a complication and its severity may influence judgement of cause and preventability. This source of bias may have led to overestimation of (preventable) complications. In addition, information was obtained from patient charts; poor quality of these charts could have led to underestimation of the incidence of complications. However, retrospective patient charts studies are currently the best method available for investigating complications.[21] Moreover, to improve the reliability of the way we identified the complications and their preventability,[22] all reviewers followed an E-learning course on complication registration and had to pass an exam.

In conclusion, our study demonstrated that complications were the reason for hospitalisation in 28.7% of all emergency admissions by internists. These complications were mostly bleeding (using anticoagulants) and infections or fever (during or after chemotherapy and/or during other immunosuppressive therapy). Although most patients recovered completely, mortality rate *during* subsequent hospitalisation was 6.3%. Interestingly, 27.8% of the complications were judged to be preventable. Moreover, almost a quarter of the complications originated in the field of other specialities than internal medicine

Registering complications in an ED is important for providing good quality of care and provides broad insight into the prevalence of complications originating during several stages of treatment provided by all sorts of doctors.

LEARNING POINTS

- Complications arise frequently, with hospitalisation being not uncommon.
- Complications are not innocent; some patients even die.
- Almost 30% of the complications are judged preventable.
- Registering complications is important for providing good quality of care.
- Registering complications in the emergency department broadens perspective.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ORAL PRESENTATION

'Registering complications at the moment of admission via the emergency department broadens perspective'. Nederlandse Internisten Dagen, MECC Maastricht, 26 April 2012. The abstract was published in the Abstract book of the Netherlands Society of Internal Medicine (NIV).

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LETTER TO THE EDITOR

Dominant type III hyperlipoproteinaemia (familial dysbetalipoproteinaemia)

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Dear Editor,

Visser *et al.*[1] describe an interesting case of a dominant form of familial type III hyperlipoproteinaemia (familial dysbetalipoproteinaemia [FD]), based on the presence of a rare APOE1 mutation. Normally, FD patients exhibit homozygosity for APOE2, which is a recessive form of dyslipidaemia, but also requires additional genetic, hormonal or environmental factors for its clinical manifestation, since only a small minority of the carriers of APOE2/E2 develop hyperlipidaemia. The hallmark of this disorder is the accumulation of atherogenic very-low-density lipoprotein (VLDL) and chylomicron remnants which can be demonstrated by an increased amount of cholesterol in the VLDL fraction (ratio of VLDL cholesterol/serum triglycerides > 0.69) after ultracentrifugation.[2] In addition to the keynotes expressed by the authors regarding their case, I would like to add two special aspects.

1) A very high level of apolipoprotein B (apoB) was measured in the patient, which the authors explained by the presence of a high level of Lp(a). This is most probably incorrect. Lp(a) is indeed an LDL-like particle in which the apoB molecule is covalently linked to a very large glycoprotein known as apolipoprotein (a) (apo a). The level of Lp(a) in plasma varies more than 1000-fold from less than 2 mg/l to more than 2000 mg/l; its measurement depends on the immunoreactivity of the apo(a) component of the protein in Lp(a).[3] Lp(a) levels are primarily genetically determined, related to the kringle IV size polymorphism with resulting number of kringle IV type 2 repeats which can vary from 3 to > 40).[4] The amount of immunodetectable apoB in Lp(a) has been reported to be less than 12%, even when Lp(a) levels were high.[5] So, there must be another reason to explain the high apoB level in this patient. We have observed earlier a variable conversion of VLDL to LDL in dominant forms of familial dysbetalipoproteinaemia.[2,6] Patients with APOE3-Leiden had on average a higher LDL-cholesterol concentration and a higher proportion of cholesterol in the LDL density range (1.019-1.063 g/ml) in n=22 E-3-Leiden carriers compared with n=24 E2/E2 carriers (38 ± 8% *vs* 23 ± 7%, p<0.0001) (Pasch, Stalenhoef, unpublished). This indicates a considerably larger amount of LDL particles in these subjects with dominant FD.

2) The use of the Friedewald formula to calculate the LDL concentration cannot be applied due to the fact that the VLDL composition is abnormal. The authors mention that the therapeutic intervention in the patient resulted in a LDL-cholesterol level of 2.96 mmol/l, which was probably calculated with this formula and is therefore incorrect.

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