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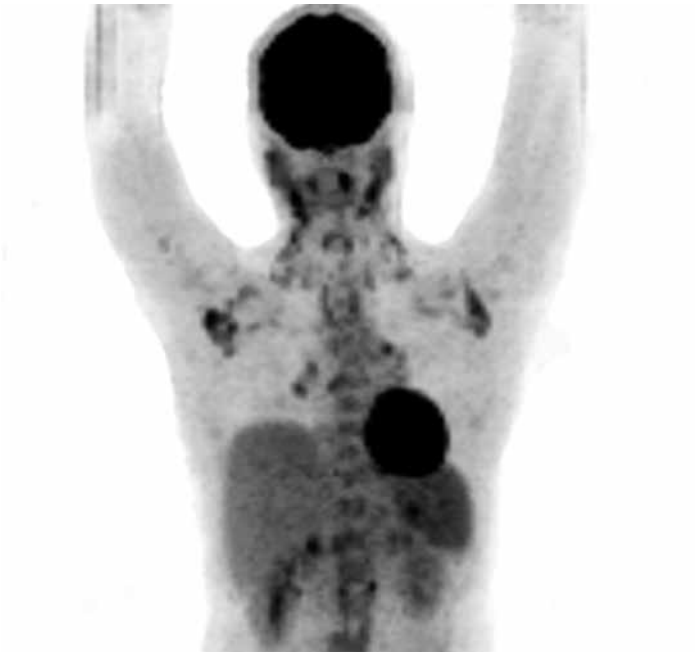

A young woman with generalised lymphadenopathy: What is your diagnosis?

Anaemia in the elderly
•
Periprocedural bridging of anticoagulation
•
Uterine artery embolisation for uterine fibroids
•
Renal transplantation in haemolytic uraemic syndrome
•
Adrenal hyperplasia due to antley-bixler syndrome
•
Implementation of the Surviving Sepsis Campaign
•
Adrenal incidentaloma with para-aortic lesions

June 2011, VOL. 69. No. 6, ISSN 0300-2977

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EDITORIAL

Anaemia in old and very old age: to be or not to be, that is not the question anymore

S.E. de Rooij

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Anaemia is common in older persons, especially in very old patients who often experience multimorbidity and may be institutionalised. Senescence, the ageing process, puts older persons at risk of developing anaemia for multiple reasons, but anaemia may not be attributed to senescence unless a thorough diagnostic workup has excluded other aetiologies. In 1994 the World Health Organisation (WHO) put an end to all suggestions that anaemia goes with old age and that reference values should be adapted for this group. Anaemia should therefore not be accepted as an inevitable consequence of ageing. A cause is found in approximately 80% of all old and very old patients. The most common causes of anaemia in the elderly patient are chronic disease and iron deficiency. Vitamin B12 deficiency, folate deficiency, gastrointestinal bleeding and myelodysplastic syndrome are among other causes of anaemia in old and very old age.

The most commonly used screening methods for the presence of anaemia in a person are the measurements of haemoglobin or haematocrit concentration (WHO 1994). These measurements are relatively simple and cheap, can be carried out under field conditions, and values below a certain cut-off point indicate or define that anaemia is likely to exist. The cut-off value defining anaemia has been determined by convention as the value at -2 SD from the mean or the 2.5th percentile of the normal distribution of a healthy population.

Even though the high prevalence of anaemia in older persons makes it a condition that physicians expect to find frequently, several features of anaemia make it easy to overlook. The onset of symptoms is often more or less insidious, and many old and very old patients adjust their activities as their bodies make physiological adaptations for their current condition. Typical symptoms of anaemia, such as an increased heart rate, fatigue, weakness and dyspnoea, are non-specific in older patients and tend to be attributed to an advancing age. In their review, Den Elzen *et al*. describe many aetiologies of anaemia in old and very old persons and thoroughly summarise the literature on a number of diagnostic and therapeutic algorithms, especially for older patients.[1] These are important as, also in old age, anaemia is associated with functional and cognitive decline, institutionalisation and mortality. But they also remark that most studies on anaemia have been performed in patients in hospital wards and residents in institutions for older persons and not in very old persons from the general population. They state furthermore that data have become available that question the extrapolation of 'common' medical knowledge to the highest age groups in this population.

Den Elzen asks for attention for normal and subnormal vitamin B12 serum levels. These situations are sometimes also associated with pernicious anaemia but do not necessarily need the same treatment regime, lifelong intramuscular vitamin B12 supplements.

Treatment of pernicious anaemia has a peculiar history: The treatment for vitamin B12 deficient anaemia was first devised by Murphy who bled dogs to make them anaemic and then fed them various substances to see what (if anything) would make these dogs healthy again. He discovered that the ingestion of large amounts of (raw) liver seemed to cure the disease. Minot and Whipple then set about chemically isolating the curative substance and ultimately were able to isolate vitamin B12 from the liver. All three shared the 1934 Nobel Prize in Medicine.

Another interesting topic brought about is hepcidin, a main regulator of iron homeostasis, which was shown to play an important role in the anaemia of (chronic) inflammation. Only recently serum hepcidin assays have become available. Besides iron, they reviewed the roles of erythropoietin, the role of telomere length in anaemia with an unknown cause, myelodysplastic syndromes or other types of bone marrow failure, and C-reactive protein and other potential biomarkers in diagnostic algorithms of anaemia in old and very old persons.

Meanwhile, geriatricians, internists and other physicians have to deal with a large number of patients with significant anaemia but also with an absence of well-constructed standards and guidelines for the old and very old patient with and without multimorbidity. The article by Den Elzen *et al*. should raise awareness that anaemia in these groups is multifactorial and that these patients are more than merely older than those included in most studies, that the results of ongoing and even future trials should be appropriately interpreted and will be important in guiding practice in the next two or three decades.

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REVIEW

Anaemia in older persons

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ABSTRACT

Anaemia is common in older individuals and, because of its association with various negative outcomes, adequate diagnosis and treatment is important. The present review focuses on prominent factors included in diagnostic and therapeutic algorithms for anaemia.

Although pernicious anaemia is associated with severe vitamin B12 deficiency, evidence of an association between subnormal vitamin B12 and anaemia in older persons in the general population is limited and inconclusive. Accumulating evidence suggests that clinicians should at least reconsider the risks of a low vitamin B12 level before starting vitamin B12 supplementation in older individuals. Although clinicians may be reluctant to measure ferritin in older individuals due to its acute phase properties, such measurements are important in older persons with anaemia, especially in those with signs of inflammation. While a severe age-related decline in renal function may lead to a blunted erythropoietin response and anaemia, elevated erythropoietin levels are associated with increased mortality. More studies are needed to identify the clinical relevance and therapeutic implications of low and high erythropoietin levels in older persons. In contrast to other age-related diseases, telomere length is not associated with anaemia in older individuals in the general population.

In conclusion, many issues regarding the aetiology of anaemia in old age remain unresolved. Because current guidelines on anaemia are based on the classic notions of the aetiology of anaemia, they may need to be revised for the highest age groups.

KEYWORDS

Anaemia, mortality, ferritin, vitamin B12, folate, erythropoietin, myelodysplasia, telomere length, aged

INTRODUCTION

Anaemia is very common in older individuals. The reported prevalence ranges from <3% in healthy persons aged ≥65 years to 61% in older patients newly admitted to geriatric wards.[1,2] This wide variance can be due to various definitions of anaemia, and to large differences in study populations with respect to gender, age, race, living situation, and health status.[1,2] In the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative study of non-institutionalised civilian adults in the USA, the overall prevalence of anaemia among adults aged ≥65 years was 11.0% in men and 10.2% in women.[3] In that study, anaemia was defined according to World Health Organisation criteria (haemoglobin concentration ≤12 g/dl in women and ≤13 g/dl in men).[4] Interestingly, the prevalence of anaemia increased significantly with age, i.e. up to 26.1% in men and 20.1% in women aged 85 years and over.[3]

In older persons, anaemia is associated with impaired survival,[5-10] decreased physical performance, disability in daily living, cognitive impairment, depression, diminished quality of life, and with an increased number of hospital admissions.[1,11-21] Considering the steep increase in the prevalence of anaemia in older individuals, and the exponential rise in the number of older individuals in our ageing society, anaemia in older individuals may have a significant impact on healthcare needs and costs in the future.[22] Adequate diagnosis and treatment of anaemia in older persons is therefore of vital importance.

In clinical practice, older patients with anaemia are carefully examined to detect and treat the underlying cause of the anaemia. Treating physicians will enquire about recent blood loss, signs and symptoms from the digestive tract, nutritional habits, weight loss, and drugs and alcohol intake.[23] In most diagnostic laboratory algorithms for anaemia, the mean corpuscular volume (MCV) plays a central role.[23-25] In patients with microcytic anaemia

(MCV <80 fl), ferritin, iron and transferrin levels are measured to determine the presence of iron deficiency anaemia. Vitamin B12 and folate are measured in patients with macrocytic anaemia (MCV >100 fl) to determine or rule out the presence of vitamin B12 or folate deficiency. Normocytic anaemias (MCV 80-100 fl) are often caused by chronic diseases, malignancies or bone marrow conditions.[23-25]

Anaemia is a unique condition in the sense that diagnostic and therapeutic guidelines are based on assumed aetiology and pathophysiology. Interestingly, most studies on anaemia have been performed in selected patient groups (e.g. patients in hospital wards and residents in institutions for older persons) and not in very old persons from the general population. Increasingly, data have become available that question the extrapolation of 'common' medical knowledge to the highest age groups. For instance, the effects of some classical determinants of disease and mortality in middle age (e.g. hypothyroidism, hypertension and hypercholesterolaemia) have been shown to disappear or even reverse in the oldest old,[26-29] indicating that physiological processes in the oldest old may be distinct from those in younger individuals.

The present review focuses on some of the most prominent factors included in diagnostic and therapeutic algorithms for anaemia to assess whether these factors also apply for older persons in the general population.

AETIOLOGY OF ANAEMIA

Vitamin B12 deficiency

Pernicious anaemia is a form of anaemia that is undeniably associated with severe vitamin B12 deficiency. Finding the cure for pernicious anaemia in fact led to the discovery of vitamin B12.[30-36] Undoubtedly, patients with very low vitamin B12 concentrations (in case of pernicious anaemia) have to be treated. Patients with pernicious anaemia or food-vitamin B12 malabsorption show large increases in haemoglobin after vitamin B12 administration.[37-40]

The outcomes of studies in patients with pernicious anaemia are often extrapolated to patients with subnormal vitamin B12 concentrations in the general population. As a result, subnormal vitamin B12 concentrations are considered to be associated with (mild) anaemia in general, but also with other conditions such as dementia, neuropathy and subacute combined degeneration of the spinal cord.[41-44] Therefore, physicians routinely measure vitamin B12 in patients with anaemia. Individuals with low serum concentrations of vitamin B12 (and normal folate concentrations) are frequently given intramuscular vitamin B12 supplements, often for many years.[23,43,44] Also, since low serum vitamin B12 concentrations are very common in older individuals,[45] screening older people for vitamin B12 deficiency has often been recommended.[46,47] However, although the biological role of vitamin B12 in haematopoiesis is well defined,[44,48-50] current evidence suggests that the outcomes of these studies in patients with severe vitamin B12 deficiency should not be extrapolated to patients with subnormal vitamin B12 concentrations in the general population.

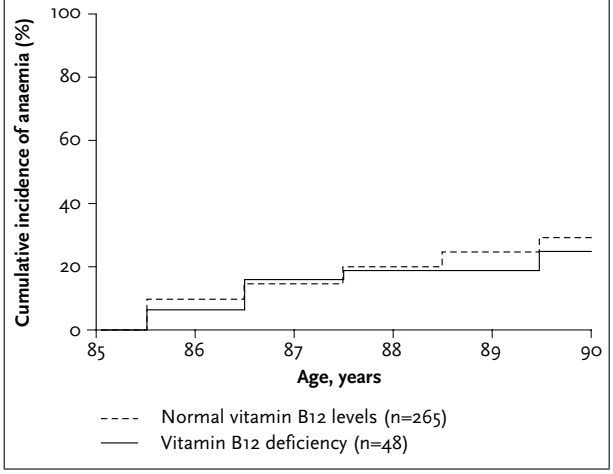
Results from the Leiden 85-plus Study

In the Leiden 85-plus Study, a population-based prospective follow-up study of 85-year-old individuals (living in Leiden, the Netherlands), we showed that low vitamin B12 concentrations (<150 pmol/l) in 85-year-old persons are not associated with the presence of anaemia at age 85 years.[51] Also, participants with low vitamin B12 concentrations did not have a higher risk to develop anaemia from age 85 onwards (*figure 1*). Adjustment for possible confounders did not change our results.[51]

Results of a systematic literature review

Interestingly, our study was not the first to cast doubt on the relationship between subnormal vitamin B12 concentrations and anaemia in older individuals. In a systematic review of the literature, we evaluated the association between subnormal vitamin B12 concentrations and anaemia in older people.[52] Twenty-two observational studies showed inconsistent results with regards to the association between subnormal vitamin B12 concentrations or vitamin B12 deficiency and anaemia in older subjects. Three randomised placebo-controlled trials (RCTs), with

Figure 1. *Effect of vitamin B12 deficiency (<150 pmol/l) on anaemia during follow-up in subjects without anaemia at age 85 years (n=313); hazard ratio 0.85; 95% confidence interval 0.43-1.65.[51] Reprinted with permission. Arch Intern Med 2008;168(20):2241. Copyright: American Medical Association. All rights reserved.*



a total of 210 participants, met the inclusion criteria for intervention studies for our review.[53-55] Due to clinical heterogeneity (differences in methods of administration, dose of vitamin B12, outcome measures and treatment follow-up time) we did not combine the results in a meta-analysis. However, the three RCTs (considered to be of methodologically high quality) showed no beneficial effect of vitamin B12 administration on haemoglobin concentrations, MCV, cognitive function and neurological symptoms.[53-55] Moreover, there was no treatment effect for participants who were anaemic.[54]

Clinical implications and implications for future research

Taking these findings into account, one may conclude that strong evidence is lacking for a positive association between subnormal vitamin B12 concentrations and anaemia in older persons in the general population. The above-mentioned findings do not imply that patients with pernicious anaemia or food-vitamin B12 malabsorption (with tissue depletion of vitamin B12 and very low vitamin B12 concentrations) should be withheld from vitamin B12 administration.[38,39] However, apart from the undisputed reality of pernicious anaemia, the clinical impact of a subnormal vitamin B12 concentration in older persons in the general population remains unclear. The fact that several observational studies and RCTs also showed no effect of vitamin B12 administration on cognitive function raises even more doubt about the consequences of subnormal vitamin B12 concentrations in older persons in the general population.[56-58]

Many older persons in primary care may receive vitamin B12 injections without evidence for clinical improvement. In addition, these findings raise doubt about the value of vitamin B12 measurement in diagnostic guidelines for anaemia as this may distract attention from other possible underlying causes. If a subnormal vitamin B12 concentration is not the cause of the anaemia, supplementation with vitamin B12 will not lead to a rise in haemoglobin concentration. Additional proof of the (lack of) effectiveness of vitamin B12 treatment in older patients with anaemia and subnormal vitamin B12 concentrations should come from a randomised double-blind placebo-controlled trial. However, before such a trial is performed, this accumulating evidence suggests that clinicians should at least reconsider the risks of a low vitamin B12 concentration before starting cyanocobalamin or hydroxocobalamin supplementation in older individuals.[59]

Interestingly, in contrast to vitamin B12, folate deficiency is still associated with anaemia in older individuals.[51] Early detection of folate deficiency by screening may identify older individuals at risk of developing anaemia. The biochemical pathways suggest that folic acid supplementation is beneficial, but it remains unclear whether folic acid fortification of grain and cereal products (as employed in the USA[60,61]) has a positive effect on the incidence of anaemia in older persons and should also be employed in the Netherlands.[62] This is a topic for future studies.

Iron deficiency and inflammation

Iron deficiency is a common cause of anaemia, being found in ≥15% of older persons with anaemia.[3,24,63] Serum ferritin levels strongly correlate with body iron stores[64,65] and are considered the best noninvasive test for the diagnosis of iron deficiency.[63,66,67] Therefore, ferritin plays a central role in diagnostic and therapeutic algorithms for iron-deficiency anaemia in clinical practice.[23-25]

Results of the Leiden 85-plus Study

Ferritin is also a well-known acute phase protein and may be elevated in acute and chronic inflammatory conditions, such as (respiratory tract) infections, rheumatoid arthritis and cancer.[63,68,69] In case of acute and chronic inflammatory conditions, serum ferritin may not accurately reflect true iron status.[63,68,69] Clinicians may be reluctant to measure ferritin in older individuals, especially in those with infections or inflammation; however, findings from the Leiden 85-plus Study suggest that ferritin measurements are important in these persons.[70] Low ferritin was associated with lower haemoglobin levels and lower MCV, but this association was more pronounced in participants with elevated C-reactive protein (CRP) levels than in subjects with normal CRP levels. It is hypothesised that low ferritin is such a specific marker of iron status in individuals with inflammation due to its 'acute phase' properties, i.e. iron status must be poor when low ferritin levels are found in the presence of inflammation.[70]

Potential role for hepcidin

It has been hypothesised that upregulation of hepcidin (the main regulator of iron homeostasis) plays an important role in the anaemia of inflammation.

An inflammatory stimulus activates monocytes and T cells to produce pro-inflammatory cytokines.[71] These cytokines, particularly interleukin 6, induce the production and secretion of hepcidin by hepatocytes.[72] Hepcidin binds to the membrane protein ferroportin, an iron efflux channel on the surface of absorptive enterocytes, macrophages and hepatocytes, and induces its internalisation and degradation in lysosomes, thereby blocking the export of iron from cells.[73] Consequently, duodenal enterocytes deliver less dietary iron to extracellular fluid, macrophages fail to release iron recycled from senescent erythrocytes and hepatocytes retain stored iron, leading to a rapid drop in iron levels,[74] iron-restricted erythropoiesis, and anaemia.[71,75,76] Moreover, transgenic mice overexpressing hepcidin and mice receiving synthetic hepcidin develop mild-to-moderate microcytic, hypochromic anaemia.[77-80]

As a result, hepcidin is considered to be the main mediator of anaemia of inflammation,[75,81,82] also known as anaemia of chronic disease, which is commonly found in patients with chronic infections or with inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, cancer and chronic kidney disease.[71,83,84] Although a preliminary analysis in the InChianti study (a population-based study of older persons in Tuscany, Italy) could not demonstrate higher urinary hepcidin levels in older individuals with anaemia of inflammation,[85] this hypothesis should still be tested in other population-based prospective follow-up studies, preferably using serum hepcidin assays which have recently become available.[86,87] Depending on the outcomes of these additional studies, future diagnostic algorithms for anaemia may incorporate markers of inflammation such as CRP or even hepcidin to discriminate between classic iron-deficiency anaemia (low hepcidin levels) and iron-deficiency anaemia in the context of anaemia of inflammation or chronic disease (elevated hepcidin levels).[87] The results of these studies may also lead to innovative clinical trials, for instance by treating older patients with anaemia of inflammation with anti-inflammatory agents or hepcidin antagonists such as agents that inhibit hepcidin production (e.g. anti-interleukin 6 receptor antibodies), hepcidin neutralising antibodies, targets against hepcidin binding site of ferroportin or agents that inhibit ferroportin internalisation.[83,88]

Erythropoietin

Renal function, erythropoietin and anaemia

Decreased oxygen availability in the kidney triggers the production of erythropoietin (the principal regulator of red blood cell mass) by the peritubular capillary lining cells within the kidney.[89] Impaired oxygen delivery to the kidney can result from various pathophysiological mechanisms, such as anaemia, hypoperfusion due to renal arteriosclerosis, lowered renal blood flow or heart failure, or decreased oxygen saturation due to diseases such as chronic obstructive pulmonary disease.[89-93] In the InChianti study, participants with a creatinine clearance of 30 ml/min or lower had significantly lower age and haemoglobin-adjusted endogenous erythropoietin levels than their counterparts with normal renal function.[94] Thus, severe age-related decline in renal function may lead to a blunted erythropoietin response and anaemia.[94] It is also known that erythropoietin substitution therapy is effective in raising haemoglobin levels and improving the quality of life in (pre) dialysis, cancer patients, and also in community-dwelling older persons with unexplained chronic anaemia.[95-99]

Erythropoietin and mortality

Interestingly, studies in chronic heart failure patients indicated that high erythropoietin is a predictor of impaired survival.[100-105] In addition, in the Leiden 85-plus Study, we also observed a dose-dependent positive association between increasing erythropoietin levels and mortality, independent of gender, creatinine clearance, haemoglobin level, comorbidity, smoking and C-reactive protein level.[106] It is not exactly clear why elevated erythropoietin levels mark excess mortality. Elevated erythropoietin levels could be a physiological response to a chronically increased hypoxic stimulus due to yet undiagnosed subclinical disease.[107,108] Elevated erythropoietin may also be compensating for removal of erythrocytes from the blood, either because of erythrocyte fragility, subclinical chronic haemolysis, or blood loss.[107,108] Further studies are needed to shed light on the mechanisms involved and to identify the clinical and therapeutic implications of a high erythropoietin level in old age, especially since a number of unexpected nonhaematopoietic functions of erythropoietin have recently been identified.[109] Our findings do not necessarily implicate that older individuals with renal failure, cancer or unexplained anaemia should not be treated with recombinant erythropoietin. However, recent meta-analyses of randomised trials showed that treatment with erythropoiesis-stimulating agents in patients with chronic kidney disease or cancer had a negative influence on survival,[110-112] which clearly emphasises the need for further studies on the aetiology and effects of high erythropoietin levels in older individuals.

Unexplained anaemia

In approximately one third of older patients with anaemia, the cause of the anaemia is unknown; their anaemia is 'unexplained'.[3] Since older subjects with unexplained anaemia often present with low leucocyte counts,[113,114] myelodysplastic syndromes or other types of bone marrow failure may be the underlying diagnosis for unexplained anaemia.[3,114-116]

Telomere length and anaemia

Telomeres are DNA-protein complexes at the ends of chromosomes. Telomeres are critical for chromosome stability and function, since they protect chromosome ends against fusion, degradation and recombination. In somatic and haematopoietic cells, telomeres shorten with every cell division as a result of the end-replication problem (i.e. the inability of the DNA replication machinery to replicate the lagging DNA strand after removal of the RNA primer) and oxidative damage.[117] Telomerase can preserve telomere length by adding *de novo* tandem repeats at chromosome ends, but its activity in somatic cells and haematopoietic progenitor cells is very low. Consequently, mean somatic cell and peripheral blood mononuclear cell telomere length shortens with age.[117] When telomere length falls below a critical level, replicative senescence (permanent growth arrest) is induced.[118,119]

Telomere length is considered a marker of biological and cellular ageing and has been correlated with a number of major age-related diseases such as dementia,[120-123] myocardial infarction,[124] heart failure,[125] atherosclerosis,[126] and solid tissue tumours.[127]

Myelodysplastic syndromes or other types of bone marrow failure are thought to explain the increased frequency of (unexplained) anaemia in older individuals.[3,115,116] Adult haematopoietic stem cells show a severe loss of telomeric DNA compared with cells from foetal liver or umbilical cord blood,[128] and aged mice have a decreased capacity to replace blood cells during haematopoietic stress compared with younger mice,[115,129] indicating a loss of replicative potential for bone marrow stem cells with age[128,130] and a possible incapacity to react to the physiological demand for blood cell replenishment with age.[115,116,129] Since earlier studies indicate that patients with myelodysplastic syndromes or other types of bone marrow failure syndromes have shortened telomeres,[131-133] shorter telomere length has been associated with an increased risk of anaemia in chronic heart failure patients[134] and was an independent predictor of lower red blood cell counts in a study of middle-aged subjects (aged 35-55 years),[135] telomere length may be a marker of haematopoietic ageing and bone marrow failure and, as a result, may be associated with anaemia in older individuals in the general population. Therefore, we investigated the relation between telomere length and the presence of anaemia (and unexplained anaemia in particular) in two population-based studies of individuals aged 85 years and over: the Newcastle 85-plus Study, and the Leiden 85-plus Study. In both cohorts, no difference was observed in telomere length between participants with anaemia and without anaemia, nor did telomere length correlate with any other haematological parameter.[136] Thus, in contrast to other age-related diseases, telomere length is not associated with anaemia or any other haematological parameter in older individuals in the general population, despite the plausible biological mechanism underlying this association. Our findings are supported by another study in which no correlation was found between telomere length and blood counts in a population-based sample of 717 women aged 38 to 100 (median 72) years.[137] To further investigate this intriguing matter, studies incorporating bone marrow biopsies are needed.

CONCLUDING REMARKS

Although researchers and clinicians have paid much attention to the clinical implications and pathophysiology of anaemia in older individuals, the consequences and underlying pathophysiological mechanisms of anaemia in the oldest old in the general population are still relatively unknown. However, it has become clear that, while folate deficiency at age 85 years is still associated with the development of anaemia during follow-up, this does not seem to be the case for vitamin B12 deficiency. Nowadays, many older subjects with subnormal vitamin B12 concentrations receive hydroxocobalamin treatment. Further trials are needed to verify whether older individuals with anaemia and subnormal vitamin B12 levels should be treated with hydroxocobalamin. Furthermore, in old age, low ferritin is associated with the presence of anaemia, particularly in older persons with elevated CRP levels, indicating that ferritin measurements are still important, especially in older persons with signs of inflammation. Serum hepcidin measurements may elucidate the complicated interrelation between iron deficiency, inflammation and anaemia. Additionally, severe age-related decline in renal function may lead to a blunted erythropoietin response and anaemia. Elevated erythropoietin levels are associated with increased mortality, independent of haemoglobin and other comorbidities. Additional studies are needed to identify the clinical relevance and therapeutic implications of a low and a high erythropoietin level in older people in the general population. Moreover, in contrast to other age-related diseases, telomere length is not associated with anaemia in older individuals in the general population, despite the plausible biological mechanism underlying this association.

Finally, future studies should focus on improving the diagnostic algorithms for anaemia in older individuals by examining the additional diagnostic value of erythropoietin, homocysteine, methylmalonic acid, CRP or hepcidin in these algorithms. Since the prevalence of anaemia is highest in the highest age groups, more studies are needed to elucidate the specific causes of anaemia in these age groups. As current diagnostic and therapeutic guidelines are based on the classic notions of the aetiology of anaemia, the guidelines on anaemia may have to be revisited for the highest age groups in the coming years.

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REVIEW

Periprocedural reversal and bridging of anticoagulant treatment

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ABSTRACT

Anticoagulants are effective agents in reducing the risk of thromboembolism but the most important adverse effect of these agents is the occurrence of bleeding. Bleeding complications may occur spontaneously but the risk of bleeding is particularly increased in case of trauma or around invasive procedures. If patients being treated with anticoagulants need to undergo an invasive intervention, physicians need to consider whether to interrupt the use of this medication or to allow its use to be continued. Suspending the use of anticoagulants increases the risk of thrombosis, whereas continued use may cause bleeding complications. To shorten the period in which anticoagulant treatment is interrupted, bridging strategies have been advocated. No evidence-based scientific research has been carried out regarding best practice for the perioperative use of anticoagulants. The periprocedural anticoagulation policy in patients should be individualised based on the risk of a thromboembolic complication (which can be estimated with available scoring systems) offset against the bleeding risk associated with the intervention.

KEYWORDS

Anticoagulants, hemorrhage, heparin, surgery, vitamin K antagonists, aspirin, clopidogrel, prasugrel, bridging

INTRODUCTION

Anticoagulant agents are often used for the prevention and treatment of a wide range of cardiovascular diseases. Most frequently used anticoagulants are heparin or its derivatives, vitamin K antagonists (such as warfarin or coumadin) and antiplatelet agents, including aspirin and thienopyridine derivatives, such as clopidogrel or prasugrel. A myriad of clinical studies have demonstrated that these agents (alone or in combination) can prevent or treat acute or chronic thromboembolic complications, in patients with atrial fibrillation or prosthetic heart valves, after myocardial infarction, percutaneous coronary interventions, or ischaemic stroke, and in patients with venous thrombosis or pulmonary embolism.[1] The most important complication of treatment with anticoagulants is haemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life-threatening.[2]

If a patient needs to undergo an urgent invasive procedure, such as emergency surgery, it may be required to reverse the anticoagulant effect of the various agents. However, in some patients reversal will increase the risk of thromboembolic complications. For such patients, the interruption of anticoagulation should be as short as possible. In many cases, so-called bridging strategies are used to shorten the duration of the period without anticoagulant cover. Depending on the clinical situation, i.e. the urgency and estimated risk of the invasive procedure, reversal may take place in a few hours, but in some cases immediate reversal is necessary.[3,4] Generally, each (immediate) reversal of anticoagulant treatment also needs to take into consideration the indication for the antithrombotic agents. For example, the interruption of combined aspirin and clopidogrel treatment in a patient in whom an intracoronary stent has recently been inserted will markedly increase the risk of acute stent thrombosis with consequent downstream cardiac ischaemia or infarction. Likewise, in a patient with a prosthetic mitral valve and atrial fibrillation, interruption of vitamin K antagonists may increase the risk of valve thrombosis and cerebral or systemic embolism. Each of these specific clinical situations requires a careful and balanced assessment of the benefits and risks of reversing

anticoagulants (and potential strategies to keep the period of reversal as short as possible). In general, the optimal periprocedural anticoagulant strategy encompasses a proper assessment of both bleeding risk associated with the intervention and the risk of a thromboembolic complication. In this manuscript we will focus on these risks, in particular for patients with atrial fibrillation, and discuss frequently used periprocedural bridging strategies.

ASSESSMENT OF THROMBOEMBOLIC RISK

The risk of a thromboembolic complication in patients with atrial fibrillation is generally estimated by means of the CHADS2 score. Based on various characteristics, namely the presence of heart failure, hypertension, age >75 years, diabetes mellitus and a history of, ischaemic stroke (ischaemic stroke) or transient ischaemic attack (TIA), one can determine the risk of thromboembolism. Patients with 0 to 2 points have an annual risk of a thromboembolic complication of 1 to 4%, whereas in patients with 3 to 6 points this is 6 to 18% per year.[5] Generally, patients with a CHADS2 score of >2 are treated with vitamin K antagonists and with lower scores by means of aspirin or without antithrombotic agents. Clinical studies have convincingly shown that treatment with anticoagulant agents in patients with atrial fibrillation substantially reduces the risk of thromboembolic complications.

There is only limited data on the perioperative thromboembolic risk. By using a large dataset of patients with atrial fibrillation who participated in a study on the outcome of restoration of sinus rhythm compared with control of ventricular rate,[6] the risk of bleeding and thrombosis around surgery in this cohort was investigated.[7] Of the 522 patients in this study 94 patients (mean 69.9 years) underwent 121 non-cardiac surgical procedures during a 29-month follow-up. In all patients the anticoagulant treatment was discontinued around the operation. In the months after surgery, no thrombotic complications occurred, compared with an incidence of 0.42%/month during the remaining months of the study (*table 1*). However, patients with atrial fibrillation and anticoagulation had a 3.6-fold increased risk of bleeding within one month after surgery. Severe haemorrhage occurred in one patient. Based on this retrospective analysis, it would appear that it is a safe policy to interrupt anticoagulation around invasive procedures in patients with atrial fibrillation. It is important to note, however, that the study population was a relatively young group in a relatively good cardiac condition. In addition, it should be taken into account that the existence of atrial fibrillation and the use of anticoagulation may have played a role in whether or not to perform surgery. The (slightly) increased risk of bleeding may be attributed to a changing institution of anticoagulant in a period after an interruption and surgery often with hospitalisation and use of various other drugs.

Table 1. *Incidence of thromboembolism and bleeding in the first month after surgery in patients with atrial fibrillation in whom the anticoagulants were interrupted compared with the incidence of these complications in a control period*

Outcome	1st month after surgery No. (% per month)	Control period No. (% per month)	Relative risk (95% CI)
Thromboembolism	0 (0)	11 (0.4)	-
Haemorrhage	3 (2.6)	19 (0.7)	3.6 (1.05-12.0)
- Major bleeding	1 (0.9)	8 (0.3)	2.8 (0.35-22.5)
- Minor bleeding	2 (1.7)	11 (0.4)	4.1 (0.91-18.4)
Both outcomes	3 (2.6)	30 (1.2)	1.2 (0.70-7.4)

95% CI = 95% confidence interval.

Notwithstanding the results mentioned above, it remains the question whether interruption of treatment in patients with a higher risk of thromboembolism could be potentially harmful.[8] In the consensus on antithrombotic treatment of the American College of Chest Physicians, stratification of patients according to their risk for perioperative thromboembolism is based on patients' clinical indication for antithrombotic therapy and the presence of comorbidities.[9] Although there is no validated risk stratification of such patients, the approach that was used in these guidelines is to separate patients into a high-risk, moderate-risk, or low-risk group according to their indication for antithrombotic therapy (*table 2*).

Table 2. *Estimated thromboembolic risk based on the ACCP consensus*

Risk stratum	Atrial fibrillation
High risk	CHADS2 score 5-6 Recent (within 3 months) stroke or TIA Rheumatic valvular heart disease Prosthetic heart valves
Moderate risk	CHADS2 score 3-4
Low risk	CHADS2 score 0-2 and no prior stroke or TIA

CHADS2 = congestive heart failure, hypertension, age >75 years, diabetes, stroke; TIA = transient ischaemic attack.

ASSESSMENT OF BLEEDING RISK

The most important complication of treatment with vitamin K antagonists (VKAs) is haemorrhage, which may be life-threatening.[2] In well-controlled patients in clinical trials treatment with VKAs increases the risk of major bleeding by 0.5%/year and the risk of intracranial haemorrhage

by about 0.2%/year.[10] The most important risk factor for haemorrhage in users of VKAs is the intensity of the anticoagulant effect.[10] Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twice as large as in studies with a target INR of 2.0 to 3.0.[11] Patient characteristics constitute another important determinant of the bleeding risk bleeding. Elderly patients have a twofold increased risk of bleeding[12] and the relative risk of intracranial haemorrhage (in particular at higher INRs) was 2.5 (95% CI 2.3 to 9.4) in patients >85 years compared with patients aged 70 to 74 years.[13] Comorbidity, such as renal or hepatic insufficiency, may also significantly increase the risk of bleeding. A case-control study in 1986 patients on VKAs showed that this comorbidity increased the risk of bleeding by about 2.5.[14] Another very important determinant of the risk of bleeding is the use of other medication, in particular agents affecting platelet function. Two meta-analyses, comprising six trials with a total of 3874 patients and ten trials with a total of 5938 patients, found a relative risk of major bleeding when VKAs were combined with aspirin of 2.4 (95% CI 1.2 to 4.8) and 2.5 (95% CI 1.7 to 3.7), respectively.[15,16]

There is no evidence that patients with atrial fibrillation have a different bleeding risk during invasive procedures compared with other patients. It may be, however, that patients with atrial fibrillation represent a relatively vulnerable population and thereby will have a somewhat enhanced risk of bleeding. Although bleeding is a treatable perioperative complication, there is emerging evidence that the clinical impact of bleeding is considerable and, perhaps, greater than previously appreciated.[9] Furthermore, postoperative bleeding delays the resumption of antithrombotic therapy, with the potential to further expose patients to an increased risk for thromboembolism. Stratifying patients according to their risk for perioperative bleeding can be based on the risk for bleeding associated with the surgery or procedure. Although there is no precise information that quantifies perioperative bleeding risk, special attention is warranted for certain surgical or other invasive procedures associated with a high risk for bleeding. These include coronary artery bypass or heart valve replacement surgery, intracranial or spinal surgery, major vascular surgery including aortic aneurysm repair or peripheral artery bypass, major orthopaedic surgery (such as hip or knee replacement), major cancer surgery and prostate and bladder surgery.

REVERSAL OF VITAMIN K ANTAGONIST TREATMENT

When interrupting the administration of VKAs important differences in the half-lives of the various agents (nine hours for acenocoumarol, 36 to 42 hours for warfarin, and 90 hours for phenprocoumon, respectively) need to be taken into account.[4,17] The most straightforward active intervention to counteract the effect of VKAs is the administration of vitamin K.[18] There is quite some debate on the use of vitamin K in patients with a too high INR who require surgery. Although a randomised controlled trial did not find any difference in bleeding or other complications in nonbleeding patients with INR values of 4.5 to 10 who were treated with vitamin K or placebo,[19] consensus-based guidelines advocate the use of small doses of vitamin K (2 mg orally) in patients with an INR >7 and using long-acting vitamin K antagonists. In patients who require subacute emergency surgery administration of vitamin K is crucial to reverse the anticoagulant effect of VKAs. Vitamin K can be given orally and intravenously, whereas the parenteral route has the advantage of a more rapid onset of the treatment.[20] After the administration of intravenous vitamin K, the INR will start to drop within two hours and will be completely normalised within 12 to 16 hours,[21] whereas after oral administration it will take up to 24 hours to normalise the INR.[18] Intramuscular injections of vitamin K should be avoided in patients who are anticoagulated and subcutaneous administration of vitamin K results in a less predictable bioavailability.[20] When the INR is below 7 a dose range of 2.5 to 5 mg of vitamin K has been advocated whereas with higher INRs a dose of 5 to 10 mg is required to correct the INR. Higher doses of vitamin K are equally effective but may lead to VKA resistance for more than a week, which may hamper long-term management.[22] A potential concern with the use of parenteral vitamin K is the occurrence of anaphylactic reactions, although the incidence of this complication is very low, in particular with the more modern micelle preparations.[23]

When immediate correction of the INR is necessary, this can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required to correct the INR is very large, carries the risk of fluid overload, and will probably take hours to administer.[24] Therefore, prothrombin complex concentrates (PCCs), most of which containing all vitamin K-dependent coagulation factors, are more useful. It should be mentioned that the exact composition of PCCs (i.e. the content of individual vitamin K dependent proteins) may significantly vary between preparations. Although PCCs can indeed be given using fixed dose schemes, it has been shown that individualised dosing regimens based on INR at presentation and body weight are more effective.[25] In a prospective cohort study of patients on VKAs who presented with major bleeding, PCCs were effective in reducing the INR below 2 in 56 out of 58 patients.[26] Another prospective study in patients using VKA and presenting with bleeding also found

that PCCs resulted in at least satisfactory and sustained haemostasis in 98%.[27] In recent years the safety of PCCs, in particular regarding the transmission of blood-borne infectious diseases, has markedly improved owing to several techniques, such as pasteurisation, nanofiltration, and addition of solvent detergent. The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from older literature and modern PCCs do not seem to be associated with eliciting DIC.[28]

REVERSAL OF ANTIPLATELET AGENTS

It has been shown that the use of aspirin is associated with increased perioperative blood loss in major procedures, although this does not necessarily translate into clinically relevant endpoints, such as the requirement for transfusion or re-operation.[29] Over the last years the approach to the patient who is taking aspirin and who presents with bleeding or needs to undergo an invasive procedure has changed considerably. In fact, in current clinical practice bleeding can almost always be managed with local haemostatic procedures or conservative strategies without interrupting aspirin and also most invasive procedures do not require the cessation of aspirin when adequate attention is given to local haemostasis. In contrast, interruption of aspirin has been associated with an increased risk of thromboembolic complications, potentially due to a rebound hypercoagulability. Obviously, in special clinical circumstances, such as the need to undergo a neurosurgical or ophthalmic procedure, the antihaemostatic effect of aspirin needs to be reversed immediately. The most rigorous measure to achieve that is the administration of platelet concentrate after cessation of aspirin. Another approach is the administration of de-amino d-arginin vasopressin (DDAVP, desmopressin). DDAVP is a vasopressin analogue that despite minor molecular differences has retained its antidiuretic properties but has much less vasoactive effects.[30,31] DDAVP induces release of the contents of the endothelial cell associated Weibel-Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII) and (also by yet unexplained additional mechanisms) a remarkable augmentation of primary haemostasis as a consequence.

Clopidogrel and prasugrel belong to the class of thienopyridine derivatives which act by blocking the adenosine diphosphate (ADP) receptor on the platelet. Importantly, the combination of aspirin and clopidogrel is vastly superior over aspirin alone in patients who have received intracoronary stents or in other patients with high-risk coronary artery disease. There is ample evidence that dual platelet inhibition of aspirin plus clopidogrel has a significantly higher efficacy than aspirin alone in patients with acute coronary syndromes who have undergone coronary interventions for at least a year (and possibly longer) after the event. However, the increased efficacy of the combined use of aspirin and clopidogrel is also associated with a significantly higher bleeding risk.[32] Prasugrel is another thienopyridine derivative that after rapid and almost complete absorption after oral ingestion irreversibly binds to the ADP receptor. Prasugrel has a stronger antiplatelet effect than clopidogrel because of more effective metabolism and less dependence of cytochrome P450 enzymes that may be subject to genetic polymorphisms.[33] The decision whether or not the interrupt or even reverse antithrombotic treatment with dual platelet inhibition in case of the need to perform an invasive procedure will depend on the specific clinical situation. Especially in patients with recent implantation of an intracoronary stent (in the last 6-12 weeks), cardiologists will often not or only reluctantly agree with cessation of treatment.[34] In this period re-endothelialisation of the stent has not yet occurred and the patient is very vulnerable to acute thrombotic occlusion of the stent. In patients with drug-eluting stents this period may be even longer. If, however, the decision is made to stop and even reverse the treatment with aspirin and clopidogrel, administration of platelet concentrate is probably the best way to correct the haemostatic defect.[35] In addition, DDAVP was shown to correct the defect in platelet aggregation caused by clopidogrel, so this may be another option.[36]

PERIPROCEDURAL ANTICOAGULATION INTERRUPTION AND/OR BRIDGING STRATEGIES IN PATIENTS WITH ATRIAL FIBRILLATION

A practical guide in selecting the most appropriate interruption and/or bridging strategy is outlined in *table 3*. In general, in patients undergoing interventions with a low risk of bleeding and major potential for adequate local haemostasis, continuation of antithrombotic treatment may be considered. In case of VKA treatment tapering the intensity of anticoagulation, for example to an INR of 1.5 to 2.0, is advocated.[9] For larger interventions, the optimal strategy is determined by the risk of thromboembolic complications when anticoagulant treatment is interrupted. In patients with low risk of thromboembolism, short-lasting interruption of anticoagulant treatment is advised. Anticoagulant treatment should not be resumed until 12 and preferably 24 hours after the intervention, to avoid bleeding complications.[37]

For patients with a high risk of thromboembolism, the window of no anticoagulant prophylaxis should be

Table 3. *Perioperative interruption and bridging strategy based on risk of thromboembolism and risk of perioperative bleeding*

Risk of thromboembolism	Risk of peri-operative bleeding: Low	Risk of peri-operative bleeding: High
High	• Consult with surgeon or operator • Continue VKA • Monitor INR • Target INR 1.5-2.0	• Stop treatment with VKA (warfarin or coumadin 3-4 days, phenprocoumon 5-7 days preoperatively) • Start therapeutic UFH or LMWH • Stop UFH 3 hrs preoperatively or LMWH 24 hrs preoperatively • Restart heparin 12-24 hrs post-operatively (if no bleeding) • Restart VKA 1-2 days postoperatively (if no bleeding) • Stop heparin when INR is in therapeutic range
Low		• Stop treatment with VKA (warfarin or coumadin 3-4 days, phenprocoumon 5-7 days preoperatively) • Restart VKA 12-24 hrs postoperatively (if no bleeding) • Usual prophylactic LMWH (prevention of venous thromboembolism)

Patients with an intermediate risk of thromboembolism are treated according to the low-risk stratum, although individual exceptions may be made based on patient characteristics and preferences of patients and doctors. VKA = vitamin K antagonists; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; INR = international normalised ratio.

minimised using heparin ('bridging'). In this strategy, therapeutic doses of heparin are administered after cessation or interruption of vitamin K antagonists. Shortly before the intervention, heparin is temporarily stopped and reinstated after termination of the procedure. The most precise bridging may be obtained by the administration of continuous intravenous unfractionated heparin, as the short half-life (about 90 minutes) may allow cessation of its administration only two to three hours before the intervention, whereas anticoagulation can be immediately resumed as soon as possible after the procedure. Also in this case it has been shown that resumption of heparin treatment before 12 to 24 hours after the intervention may lead to major bleeding complications.[38] The disadvantage of this strategy with unfractionated heparin is that it requires intravenous treatment, thereby potentially prolonging the hospital stay, and the variable intraindividual and interindividual effect, necessitating frequent laboratory monitoring with sequential aPTTs. An alternative to unfractionated heparin may be low-molecular-weight (LMW) heparin, which may be administered subcutaneously and has a more predictable anticoagulant effect. Bridging strategies with LMW heparin may be performed in an outpatient setting and in general do not require laboratory monitoring. The disadvantage of LMW heparin is its relatively longer half-life (8 to 12 hours), which may make it somewhat more difficult to precisely plan cessation of this agent relative to the timing of the intervention.

For patients with an intermediate risk of thromboembolic complications it is hard to formulate clear guidelines. Especially in this area individualised treatment decisions should be made in close consultation between cardiologist, haemostasis specialist, and surgeon. Most local guidelines now advocate to treat intermediate-risk patients as low-risk patients; however, in individual cases and dependent on the intervention, clinical circumstances, and preferences of patients and doctors, it seems justified to follow a bridging rather than an interruption strategy in selected patients.

CONCLUSION

The periprocedural anticoagulation policy in patients with atrial fibrillation should be individualised based on the risk of a thromboembolic complication offset against the bleeding risk associated with the intervention. A proper assessment should be made of the perioperative risk of thromboembolism after discontinuation of anticoagulant therapy versus the bleeding risk due to continuing this treatment around the invasive procedure. In case of a high risk of thromboembolic complications and a procedure with a high bleeding risk, bridging of anticoagulant treatment with heparin or LMW heparin to interrupt anticoagulant prophylaxis as short as possible should be considered.

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ORIGINAL ARTICLE

Implementation of uterine artery embolisation for symptomatic uterine fibroids: an inventory

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ABSTRACT

The validity of uterine artery embolisation (UAE) as an alternative treatment for hysterectomy to treat symptomatic uterine fibroids has been well established. Despite its favourable outcomes, UAE is still only marginally applied in the Netherlands. The aim of this inventory is to identify factors which either restrict or facilitate the implementation of UAE.

Gynaecologists and interventional-radiologists in three hospitals in Amsterdam were interviewed by means of questionnaires. One of these hospitals had ample experience in UAE for uterine fibroids, one hospital had just started providing this treatment, and one hospital did not perform UAE. Also patients with symptomatic fibroids who were scheduled for either UAE or hysterectomy were interviewed about the counselling for UAE.

The following obstacles in the implementation of UAE were found: lack of knowledge about UAE, absence of a multidisciplinary protocol, and above all, the absence of UAE as one of the treatment options in the Dutch national guideline on the management of menorrhagia. 75% of all patients claimed to be well informed about UAE by their gynaecologist.

Our recommendations for the implementation of UAE are: 1) adding UAE to the Dutch guideline for the management of menorrhagia with clearly defined indications and contraindications; 2) educating gynaecologists about UAE; 3) composing a patient information leaflet and a website, and 4) arranging a protocol in a multidisciplinary team.

KEYWORDS

Uterine artery embolisation, uterine fibroids, implementation

INTRODUCTION

Since the introduction of uterine artery embolisation (UAE) for symptomatic uterine fibroids by Ravina *et al.* in 1995[1] the effect of UAE on shrinkage of fibroids and reduction of symptoms became evident. Three randomised studies evaluated various aspects of this new treatment modality and demonstrated its equivalence and -sometimes- superiority to hysterectomy and/or myomectomy.[2-6] Even after five years of follow-up, UAE was found to be equally effective compared with hysterectomy in terms of patients' Health Related Quality of Life (HRQOL) and satisfaction, while its cost-effectiveness was superior.[7] Despite these favourable outcomes of UAE, its implementation in daily practice has been rather disappointing, as illustrated by a recent CIRSE (Cardiovascular and Interventional Radiological Society of Europe) survey.[8] This survey illustrates that although the use of UAE was widespread throughout European countries in 2009, the majority of centres (53%) performed only between 10 and 50 UAE procedures/year. They stated the importance of using the media to enhance patient awareness of treatment options such as UAE and that the creation of an interactive website is a unique opportunity to do so. The survey also recommended UAE to be offered as part of a multidisciplinary approach, thereby including radiologists, gynaecologists and anaesthesiologists. However, no further advice was given on how to implement UAE in routine practice. To analyse all the possible restricting and facilitating factors in the implementation of UAE and to put forward recommendations for wider use of UAE in the treatment for symptomatic uterine fibroids we performed an inventory among a group comprising an interventional-radiologist, gynaecologists and patients suffering from symptomatic uterine fibroids in three hospitals in Amsterdam.

METHODS

This inventory was performed between March 31st and June 15th 2010 and consisted of questionnaires and interviews. It was performed in three (non-academic) hospitals in Amsterdam; one hospital with ample experience with UAE for uterine fibroids, one hospital that had just started providing this treatment, and one hospital where UAE is not being performed. The experience in UAE, and the size and setting of these hospitals differed.

Questionnaires and interviews

The questionnaires for the gynaecologists were composed by investigators of the EMMY (EMbolization versus hysterectoMY) trial[4-7] after interviewing a gynaecologist specialised in the treatment of fibroids in each participating hospital. The questionnaires were quite similar to the questions in the interviews, but they were shorter for optimising the response rate, and were administered to all gynaecologists of the three hospitals. In both the hospitals offering UAE, the intervention-radiologist specialised in performing UAE was interviewed. The reason to interview only one radiologist per hospital was that the counselling process starts with the gynaecologist when patients visit the outpatient clinic for heavy menstrual bleeding caused by fibroids. Therefore interviewing the radiologists was to survey the process after the counselling by the gynaecologist.
In both the interviews and questionnaires various determinants were examined concerning UAE: knowledge, experience, attitude towards the procedure, expectations, logistics and financial and educational considerations.[9,10] The questions were designed to identify which determinants are relevant in the implementation of UAE.

Gynaecologists

The questionnaires for gynaecologists concerned: 1) the counselling process; 2) perceived (contra) indications for UAE; 3) how often patients were referred for UAE; 4) whether they feel sufficiently informed about the procedure; 5) the restricting and facilitating factors in implementation of UAE for fibroids in the Netherlands, and 6) based on existing literature about implementation strategies, we selected existing strategies and asked whether the gynaecologist judged the following strategies would contribute to a successful implementation: a) adding UAE to the Dutch guideline on the management of menorrhagia; b) organising a conference or information meeting for gynaecologists; c) creating a patient information leaflet and website on UAE; d) approaching key figures in the gynaecological department to spread the knowledge about the procedure.[11-14]

Radiologists

The questions in the interviews with radiologists in the two hospitals concerned: 1) whether or not radiologists should be involved in the counselling of patients eligible for UAE; 2) any foreseeable problems which might arise in practice when doing so; 3) their personal experience with performing UAE; 4) the restricting and facilitating factors in implementation of UAE for fibroids in the Netherlands and 5) whether the above-mentioned implementation strategies would contribute to the implementation of UAE.

Interviews with patients

We conducted structured interviews with patients scheduled for UAE or hysterectomy for symptomatic uterine fibroids in the three hospitals. All patients who were scheduled for UAE or hysterectomy between March 31st and June 15th 2010 were asked to participate if they were pre-menopausal and did not have a wish for future pregnancy. If informed consent was obtained, they were interviewed prior to the procedure.

UAE patients

The questions for patients undergoing UAE addressed the following subjects: 1) if and where they had learned about UAE; 2) their satisfaction about the information received from the gynaecologist; 3) whether they had received an information leaflet, and 4) why they had opted for UAE. Several options were mentioned and patients were asked if these applied to their situation.

Hysterectomy patients

Patients eligible for UAE who underwent a hysterectomy for symptomatic uterine fibroids were interviewed in all the participating hospitals in the same period. The questions addressed the following: 1) whether they were offered an alternative to hysterectomy; 2) which alternative(s) was/were offered; 3) the information received about UAE and 4) why they had opted for hysterectomy.

RESULTS

Questionnaires were sent to 24 gynaecologists and two interventional radiologists. Seventeen gynaecologists returned the questionnaires, including two of the three interviewed gynaecologists. For this reason some questions are answered by 17, and some by 18 gynaecologists. Only two interventional radiologists were interviewed, i.e. the specialists who perform the UAEs in the two hospitals providing UAE.
Most gynaecologists (14/18, 77.8%) shared the opinion that UAE should be a standard treatment option to offer a patient with symptomatic uterine fibroids if the patient

meets the inclusion criteria. There are criteria, however, that some gynaecologists consider to be an exclusion criterion for UAE, while others do not. A submucous fibroid was considered to be an exclusion criterion by 23.5% (4/17), while patients with fibroids without menorrhagia were not counselled for UAE by 41.2% (7/17). Almost all gynaecologists (17/18, 94.4%) declared that they had adequate knowledge about UAE for counselling their patients. Some gynaecologists (8/18, 44.4%), however, indicated they were uncertain about several aspects of UAE about which they needed more information, especially on the effect of UAE on uterine fibroids on specific localisations and on the effect of UAE on fertility.

In one of the two hospitals where UAE is performed, counselling by the attending interventional-radiologist is part of the standard counselling process and most (11/16, 68.8%) of all gynaecologists and radiologists in these two UAE performing hospitals find it necessary to work in a multidisciplinary team. Both radiologists said they were well educated about UAE and had ample experience in performing the procedure. Most gynaecologists (11/14, 78.6%) indicated that they referred patients for UAE more often since the procedure was offered in their hospital. The gynaecologists of the hospital where UAE is not performed mentioned that they would not refer more often if the procedure was being offered in their hospital, as stated by 75% (3/4). At this moment they refer their patients to an academic centre in Amsterdam if UAE is indicated. Both gynaecologists and radiologists mentioned that streamlining the procedure and making a postprocedural pain protocol in a multidisciplinary team would improve the logistics.

The gynaecologists indicated the following factors to restrict the implementation of UAE:

- Lack of knowledge of the procedure in a group of gynaecologists, which might lead to less counselling (3/18, 16.7%).
- Some gynaecologists (2/18, 11.1%) have the opinion that many gynaecologists do not believe in favourable results of UAE and that they therefore do not counsel.
- Concerns that the number of surgical procedures performed by gynaecologists might decrease with financial consequences for the gynaecological department (3/18, 16.7%).
- Concerns about the development of surgical skills by residents because of dropping numbers of hysterectomy (3/18, 16.7%).

The gynaecologists indicated the following factors to facilitate the implementation of UAE:

- Adding UAE to the Dutch guideline on the management of menorrhagia (16/18, 88.9%).
- Appointing 'key figures' in the gynaecological department to spread the knowledge about UAE (14/18, 77.8%).
- Organising conferences or information meetings about UAE in order to improve the knowledge on UAE among gynaecologists (13/18, 72.2%).
- The formation of a multidisciplinary team to formulate logistic procedures, pain management and an after-care protocol, in order to improve the cooperation between the radiology and gynaecology department (11/18, 61.1%).
- Development of agreement between the gynaecology and radiology departments about proper financial arrangement in offering UAE (1/18, 5.6%).
- Selecting centres that will offer the procedure and announcing this to all hospitals in the Netherlands, so that every gynaecologist knows where to refer to (2/18, 11.1%).
- A patient information leaflet and website (18/18, 100%).
- Publication of success stories of satisfied patients for fellow patients, gynaecologists and interventional-radiologists (2/18, 11.1%).

Both radiologists indicated the following factors to restrict the implementation of UAE:

- Gynaecologists are not sufficiently convinced about the results of UAE in the treatment of fibroids.
- Radiologists should be more part of the follow-up of the patients after UAE.
- No streamlined protocol on logistics, pain management and aftercare after the procedure.

Both radiologists indicated the following factors to facilitate the implementation of UAE:

- Implementation of UAE for fibroids in the Dutch guideline on the management of menorrhagia.
- Gynaecologists need to be better informed about UAE, for example in congresses or meetings.
- Creating a patient information leaflet and website on UAE.
- Approaching 'key figures' in the gynaecological department to spread the knowledge about the procedure.
- The protocol needs to be streamlined, especially a logistics, pain management and after-care protocol for each specific hospital that offers UAE, made by a multidisciplinary team.

Patients

All patients were premenopausal women who suffered from menorrhagia due to fibroids that were not removable by transcervical resection or by laparoscopy. They did not have contraindications for UAE, had no desire for future pregnancy and informed consent was obtained.

UAE patients

All eight patients scheduled for UAE were satisfied about the information they received on UAE. Most of them learned about UAE from their gynaecologist (5/8, 62.5%; 95% CI 24.5 to 91.5) while some (3/8, 37.5%; 95% CI 8.5 to 75.5) found information on the internet, after which they discussed this option with their gynaecologist. All patients said they would have liked to receive an information leaflet about the procedure, but even without this leaflet they said they were well-informed about the procedure (8/8, 100%; 95% CI 63.1 to 100), the hospital stay (7/8, 87.5%; 95% CI 47.3 to 99.7), the recovery period (7/8, 87.5%; 95% CI 47.3 to 99.7), and possible complications (7/8, 87.5%; 95% CI 47.3 to 99.7). The most important reason for them to choose UAE over a hysterectomy was a shorter hospital stay (4/8, 50%; 95% CI 15.7 to 84.5), preservation of the uterus (7/8, 87.5%; 95% CI 47.3 to 99.7), because UAE was viewed as less invasive without abdominal scars (5/8, 62.5%; 95% CI 24.5 to 91.5) and because they liked the fact that they could resume work sooner (5/8, 62.5%; 95% CI 24.5 to 91.5).

Hysterectomy patients

Of the seven hysterectomy patients suitable for UAE, 85.7% (6/7; 95% CI 42.1 to 99.6) received information about UAE. All of them said that the main reason for choosing hysterectomy was its definitive character in solving of their problem. Some stated that they preferred to be treated by their own gynaecologist (5/7; 71.4%, 95% CI 29.0 to 96.3) or the possibility to be treated in their own hospital (2/7; 28.6%, 95% CI 3.7 to 71.0) as a reason to choose for hysterectomy.

DISCUSSION

In this inventory we analysed the factors restricting or facilitating the implementation of UAE in the treatment of symptomatic uterine fibroids in Amsterdam. UAE is a proven valuable alternative to hysterectomy, but still neither implemented well in Amsterdam, nor in the Netherlands, or in Europe.[8] Implementation strategies for new medical treatments in general have been widely studied. The majority of these studies concluded that effective implementation strategies included multifaceted interventions (interventions composed of a varied range of components or strategies) and interactive education. Multifaceted interventions consistently resulted in significant improvements in guideline compliance and behavioural change.[12,15,16] Interactive education strategies including workshops and practical sessions are also effective. The most important reported effects attributed to educational strategies are associated with educational outreach visits by educators, the provision of promotional material and subsequent reminders or educational follow-up.[17-19] Thus knowledge about the procedure by health care providers is most important in the implementation of a new procedure. This is more or less in accordance with this inventory. The factors that we found as restricting the implementation of UAE almost all had to do with ignorance about the procedure. Although almost all of the gynaecologists who were questioned claimed to have enough knowledge on UAE, some mentioned a lack of knowledge among gynaecologists as a restricting factor. The most important conclusion in our study is that UAE has to be implemented in the Dutch guideline on the management of menorrhagia first, before it can be implemented in the treatment spectrum for symptomatic uterine fibroids in the Netherlands. This guideline should contain information on inclusion and exclusion criteria, effectiveness and on the effect of UAE on pregnancy because these are subjects some gynaecologists are not convinced about. A submucous fibroid, for example, was considered to be an exclusion criterion by 23.5% because of the possible risk of necrosis and infection,[20] while patients with fibroids without menorrhagia were not counselled for UAE by 41.2%, because they stated that for patients suffering from only bulk and pressure symptoms caused by fibroids a hysterectomy might be more effective. Although UAE has already been implemented in the NICE guideline on menorrhagia, adding UAE to the Dutch (NVOG) national guideline on menorrhagia will reach more gynaecologists in the Netherlands.

In the interviews many professionals expressed the need for standardised protocols on pain management and after-care in UAE, which ideally should be streamlined by a multidisciplinary team with a gynaecologist, interventional-radiologist and anaesthesiologist. Patients expressed the requirement for further information, i.e. leaflets and a website, as an addition to the counselling process. Another obstructing factor is possible financial loss; some gynaecologists mentioned 'losing' their patients to the intervention-radiologists, with financial consequences. A resolution for this financial problem might lie in constructing a joint billing system, in which both specialities will have their proportional financial share. Another option for the financial motives is to convince the gynaecologists that it might actually be financially beneficial to offer UAE. Being able to offer the complete range of treatments (either in their own hospital or by referral to another hospital) makes a hospital an appealing treatment centre and will therefore attract more patients for the gynaecology department.

There are some limitations to this inventory. Firstly the number of interviewed interventional-radiologists was very limited. We decided to interview the UAE specialist in both UAE performing hospitals, because the counselling of patients on UAE primarily occurs

by the gynaecologists. Secondly we did not use existing questionnaires on implementation, because these were not available. Our questionnaires might be useful in the rest of the Netherlands to perceive a broader perspective of the problems that need to be solved before UAE can be implemented as a fully accepted option for the treatment of symptomatic uterine fibroids.

In summary, our recommendations to facilitate implementation of UAE are: 1) adding UAE to the Dutch guideline for treatment of menorrhagia with clearly described indications and contraindications; 2) educating gynaecologists about UAE, for example by organising a conference or information meeting; 3) composing a patient information leaflet and a website, and 4) arranging clear agreements between the gynaecology and radiology departments in a multidisciplinary team.

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CASE REPORT

Renal transplantation in patients with atypical haemolytic uraemic syndrome: a tailor made approach is necessary

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ABSTRACT

A 33-year-old woman with a history of chronic transplant dysfunction because of repeated bouts of haemolytic uraemic syndrome (HUS) was considered for a second transplant. Extensive genetic investigation of the complement system was executed to rule out known mutations prone to development of HUS. This case illustrates the importance of genetic screening in patients with recurrent HUS.

KEYWORDS

Atypical haemolytic uremic syndrome, transplantation, factor H

INTRODUCTION

HUS is a disorder characterised by thrombotic microangiopathy (TMA) with thrombocytopenia, haemolytic anaemia and renal failure. Two different forms can be described. The typical form is usually associated with food-borne infections with Shiga-like toxin producing *Escherichia coli* O157:H7 (*E. coli* O157:H7) causing diarrhoea and in approximately 6% end-stage renal failure (ESRD); however, the long-term prognosis is good. Atypical HUS (aHUS), is most frequently seen in adults and is not caused by infection with the toxin-producing *E. coli*. The prognosis is less favourable, up to 50% progress to ESRD.[1] Dysregulation of the complement system due to mutations in its inhibitors can be found in the majority of cases of aHUS. In the presence of certain triggers this causes unrestrained complement activation.[2]

Mutations can be divided into two groups: mutations in inhibitor proteins circulating in plasma and mutations of inhibitors that are membrane bound. Atypical HUS caused by mutations of the membrane bound protein (MCP) has a good prognosis but mutations in plasma factors factor H (CFH) or factor I (CFI) are known to have a poor prognosis as well as a high recurrence rate of HUS in the transplant.[3-5] We present a case where a patient with a factor H polymorphism was successfully transplanted with pre- and postoperative plasmapheresis and infusion of fresh frozen plasma (FFP).

CASE REPORT

A 33-year-old woman was referred to our hospital because of a considered second renal transplantation due to failure of the first transplant, which she received when she was 13 years old. The initial diagnosis was ESRD due to IgA nephropathy (also in retrospect without signs of TMA).
Because of two proven episodes of HUS we suspected a possible dysfunctioning complement system which consequently was thoroughly investigated. Levels of her complementary proteins C3 and C4 were both within normal range. Factor B was low: 72 mg/l (90 to 320 mg/l) and factor I was measured at 71% (expressed as percentage of normal: 70-130%). The levels of her factor H were normal, being 120% (65 to 140%). Also, no antifactor H antibodies were detectable. However, six heterozygote DNA polymorphisms were found on the gene encoding for factor H.[6] Of these, the polymorphism c.2016A>G in exon 14 and c.2881G>T in exon 19 have been proven to be associated with the development of HUS.[7]

Initially her HLA-matching sister was willing to donate her kidney; however, because family members of patients with abnormal factor H have higher risks of having complement abnormalities themselves, she was not considered eligible as a possible donor. Most fortunately, a living unrelated donor was available.

At the time of admission, serum creatinine was as high as 634 µmol/l, serum urea 30.9 mmol/l her haptoglobin was as low as <0.2 g/l and complement C3 0.56 g/l.

To prevent postoperative recurrence of aHUS we started preoperative plasma exchange therapy with infusion of FFP. Plasma exchange of 1.5 times the plasma volume was continued postoperatively once a day for the first week, every other day the next week and twice in the third week. It was stopped after a total of 13 procedures at day 23. Immunosuppression after transplantation consisted of tacrolimus 3 mg twice daily, mycophenolate mofetil 2 g twice daily and low-dose prednisolone (20 mg once daily, rapidly tapered to 10 mg). She was discharged from the hospital on day 28 after transplantation in a good condition, with no signs of recurrence of HUS and a serum creatinine of 90 µmol/l. Now, three years later, her renal function is still excellent with a serum creatinine of 84 µmol/l.

DISCUSSION

A feature underlined by this case but already proven in several other cases is that no patient suffering from aHUS should be transplanted without additional measures. There has been some experimenting with several modalities of treatment in aHUS. When caused by autoantibodies against factor H plasmapheresis alone has been proven efficient because the antibodies are then removed from the circulation.[8] However, when aHUS is caused by a mutation in factor H or factor I this is not sufficient and infusion of FFP containing large amounts of factor H and I will be necessary. When there is a total deficiency of factor H a combined kidney and liver transplantation has been recommended. In that case, it is also indispensable to take preoperative as well as postoperative measures given the massive complement activation during ischaemia reperfusion, which cannot be counteracted since initially the freshly transplanted liver is not capable of synthesising sufficient amounts of factor H, resulting in primary non-functioning of the liver.[9,10]

It is essential in all of these cases to realise that only approximately 50% of all mutations causing HUS have been discovered. Two cases of HUS in the donor have been described very short after donation in which no (as yet established) mutations in the regulatory complement inhibitors could be identified.[10] For that reason it is strongly advised not to perform a living donor transplantation with a family member as donor, even if genetic screening reveals no mutations in their complement inhibitors.[11]

The need for a trial of complement inhibitors, such as eculizumab, now already used in trials for acute aHUS and plasma-resistant HUS, is definitely warranted in the future.[12] The options of using recombinant factor H are also being investigated and promising results have already been published (*in vitro* studies).[13]

In conclusion, this case report describes the importance of investigating the complement profile including genetic screening in patients with aHUS and gives a schedule for plasma exchange therapy with infusion of FFP. Family members cannot be used as donor, even when the recipient has a sporadic form of HUS as original disease.

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CASE REPORT

A rare cause of congenital adrenal hyperplasia: Antley-Bixler syndrome due to POR deficiency

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ABSTRACT

Cytochrome P450 oxidoreductase (POR) deficiency is a recently discovered new variant of congenital adrenal hyperplasia. Distinctive features of POR deficiency are the presence of disorders of sexual development in both sexes, glucocorticoid deficiency and skeletal malformations similar to those observed in the Antley-Bixler syndrome.

KEYWORDS

Antley-Bixler syndrome, congenital adrenal hyperplasia, POR deficiency

INTRODUCTION

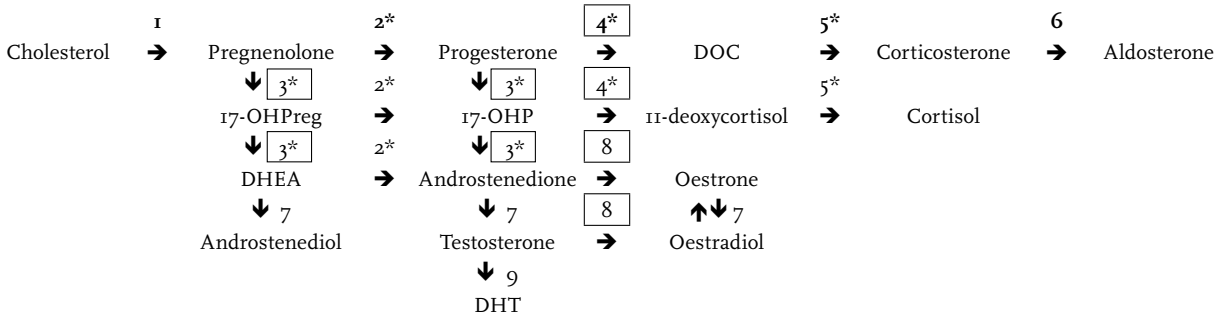
Congenital adrenal hyperplasia (CAH) comprises a group of inherited autosomal recessive disorders characterised by a defective cortisol biosynthesis, compensatory increases in corticotrophin secretion and adrenocortical hyperplasia. Cardinal symptoms of CAH are adrenal insufficiency, disorders of sexual development (DSD), short stature and infertility.[1] The most frequent cause of CAH is 21-hydroxylase (CYP21A2) deficiency, which is responsible for about 95% of cases (*figure 1*).[2] Other causes of CAH are deficiency of 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), 17α-hydroxylase (CYP17A1) or 11β-hydroxylase (CYP11B1). Furthermore, two distinctive CAH variants are not caused by defective synthesis of a steroidogenic enzyme, but result from decreased enzyme activity due to the deficiency of an important co-factor. Lipoid CAH is caused by loss-of-function mutations in the gene encoding steroidogenic acute regulatory protein (StAR), which facilitates cholesterol transport from the outer to the inner mitochondrial membrane, thus providing the substrate for steroid biosynthesis.[3] More recently, cytochrome P450 oxidoreductase (POR) deficiency has been identified as a new CAH variant.[4,5]

CASE REPORT

A 19-year-old female was referred for evaluation of irregular menses. As a neonate, she had been examined at the Department of Clinical Genetics for several dysmorphic features. At the time, her karyotype had been documented as 46,XX; a specific diagnosis had not been attained and she had been lost to follow-up. She did not report any other complaints, except for a lack of libido. Her parents were non-consanguineous. At physical examination, blood pressure was 128/64 mmHg, height 182.5 cm (+1.98 SD), body weight 88 kg (+3.1 SD) and body mass index 26.3 kg/m^2 (+1.5 SD). Axillary and pubic hair were sparse. Breast development was normal, but internal labia appeared infantile (Tanner stage: B5,P3). Several dysmorphic features were observed: prominent forehead, midface hypoplasia with depressed nasal bridge, pear-shaped bifid nose, small mouth with high-arched palate, limited supination of forearms, long slender hands, extension contractures of metacarpal joints and irregularly positioned toes.

Hormonal analysis in serum revealed a distinct pattern: 17-hydroxyprogesterone 17 nmol/l (reference: 2.0 to 8.0 nmol/l), androstenedione 0.6 nmol/l (3.0 to 9.6 nmol/l), dehydroepiandrosterone (DHEA) 1.2 μmol/l (3.0 to 13.0 μmol/l), oestradiol 0.09 nmol/l (follicular phase: 0.07 to

Figure 1. *Schematic overview of adrenal and gonadal steroid biosynthesis and their enzymes.*



Most of these enzymes belong to the family of cytochrome P450 oxygenases (CYP). Steroidogenic acute regulatory protein (StAR) facilitates the movement of cholesterol from the cytosol into the mitochondria, where it is converted to pregnenolone by P450 side-chain cleavage enzyme (CYP11A1). This reaction is the rate-limiting step in steroid biosynthesis. Each number represents a steroidogenic enzyme. Numbers with an asterisk represent enzymes involved in the classical enzyme deficiencies of congenital adrenal hyperplasia. Numbers within a box represent enzymes requiring electron transfer from P450 oxidoreductase. DOC = deoxycorticosterone; 17OHPreg = 17-hydroxypregnenolone; 17-OHP = 17-hydroxyprogesterone; DHEA = dehydroepiandrosterone. 1 = StAR and P450 side-chain cleavage enzyme (CYP11A1); 2 = 3β-hydroxysteroid dehydrogenase (HSD3B); 3 = 17α-hydroxylase/17,20-lyase (CYP17A1); 4 = 21α-hydroxylase (CYP21A2); 5 = 11β-hydroxylase (CYP11B1); 6 = aldosterone synthase (CYP11B2); 7 = 17β-hydroxysteroid dehydrogenase type 3 (HSD17B3); 8 = aromatase (CYP19A1); 9 = 5α-reductase type 2.

0.53 nmol/l), luteinising hormone 6.15 IU/l (2.1 to 14.0 IU/l) and follicle-stimulating hormone 10.0 IU/l (1.8 to 9.6 IU/l). In addition, urinary gas chromatography/mass spectrometry (GC/MS) demonstrated decreased metabolite excretion of androgens and elevated metabolite excretions of progesterone, 17-hydroxyprogesterone and corticosterone. Serum cortisol before and after intravenous administration of 250 µg cosyntropin (synthetic $ACTH_{1-24}$) was 375 and 425 nmol/l, respectively (normal response >500 nmol/l). An abdominal MRI demonstrated cystic enlargement of her right ovary, but was otherwise normal. Sequencing of the POR gene revealed a missense mutation in exon 4 (g.26404A>G, p.T142A) of one allele and a frameshift mutation in exon 10 leading to a stop codon (g.30843dupC, p.Y376LfsX74) in the other allele. Treatment with oestradiol-dydrogesterone and DHEA was instituted and hydrocortisone coverage for medical stress situations was advised.

DISCUSSION

POR deficiency has only recently been identified as a separate CAH variant. The first patient was described in 1985, representing a 46,XY newborn with DSD and impaired steroid biosynthesis compatible with defective activities of CYP21A2 and CYP17A1.[6] The underlying mechanism, however, remained elusive for many years. DNA analysis of CYP21A2 and CYP17A1 revealed no mutation.[7,8] Sequencing of the POR gene became feasible through its description in the human genome project, resulting in the identification of POR gene mutations in these patients.[4,5] Until now, more than 40 mutations have been found in about 70 cases with POR deficiency. The POR gene is located on chromosome 7q11.2 and consists of 15 exons. It encodes a flavoprotein which facilitates electron transfer from NADPH to microsomal bound cytochrome P450 enzymes, including the steroidogenic enzymes CYP21A2, CYP17A1 and CYP19A1.[9] A variety of inactivating mutations have been described, including missense, frameshift and splice site mutations.[1] The missense mutation in our patient was also present in her father and has been described before.[10] The frameshift mutation represented a *de novo* mutation and has not been described in a previously reported patient.

Clinically, POR deficiency is characterised by DSD, glucocorticoid deficiency and skeletal malformations. In contrast to other CAH variants, DSD may be present in both sexes. Male undervirilisation is readily explained by inhibition of CYP17A1, leading to decreased production of androgens. Female virilisation despite low circulating androgen levels is a more puzzling finding that might be explained by the presence of an alternative pathway towards androgen synthesis which is only active during foetal life.[4] The glucocorticoid deficiency is often partial, and should be actively sought for by performing a cosyntropin stimulation test. Skeletal malformations closely resemble those observed in Antley-Bixler syndrome with features such as craniosynostosis, brachycephaly, midface hypoplasia, radiohumeral synostosis, radio-ulnar synostosis, choanal atresia or stenosis and multiple joint contractures.[4,11] These are probably caused by impaired

synthesis of cholesterol and retinoic acid metabolism, both of which play a crucial role in the regulation of foetal bone development and growth. Antley-Bixler syndrome is genetically heterogeneous and can also originate from autosomal dominant inherited mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene, which are not accompanied by abnormalities in steroid biosynthesis.[8] Recently, ovarian cysts have been described in several girls with POR deficiency.[12,13] These may be driven by high gonadotropins, but possibly also by impaired CYP51A1-mediated production of meiosis-activating sterols due to mutant POR.[12]

The diagnosis of POR deficiency is established by urinary steroid profiling with GC/MS, which reveals a characteristic accumulation of pregnenolone and progesterone metabolites, combined with low androgen metabolites and increased 17-hydroxyprogesterone metabolites. If urinary steroid profiling is not directly available, the combination of an increased serum 17-hydroxyprogesterone level with low serum levels of sex steroids may suggest the presence of POR deficiency. However, analysis of serum steroids may be misleading, as several combinations of serum steroids have been described.[14] As in our patient, an increased excretion of corticosterone metabolites might be present, reflecting the preferential inhibition of CYP17A1 over CYP21A2, which has been described in certain POR mutations.[15] Treatment consists of sex hormone replacement and regular hydrocortisone treatment or stress coverage only, depending on the degree of adrenal insufficiency. In addition, genetic counselling should be offered and orthopaedic management of the skeletal malformations might be indicated in some patients.

CONCLUSION

POR deficiency is a recently recognised CAH variant characterised by distinctive features such as DSD in both sexes and skeletal malformations. Urinary steroid profiling should be considered in all patients with features of Antley-Bixler syndrome.

ACKNOWLEDGEMENT

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Netherlands
The Journal of Medicine

PHOTO QUIZ

A young woman with generalised lymphadenopathy

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CASE REPORT

A 25-year-old woman of Dutch origin was referred to the outpatient clinic of a university medical centre because of generalised lymphadenopathy, anaemia, and thrombocytopenia. The patient had been healthy until three months ago. She had visited her general practitioner because of a red and painful eye. She insisted on a blood analysis, which revealed an abnormal blood count. There were no complaints of fever, weight loss, bleeding diathesis, arthralgias, exanthema or night sweats. She had no relevant medical history. Her eye complaints disappeared spontaneously after a few days.

Physical examination showed submandibular, axillary and inguinal bilateral lymphadenopathy, with elastic, small (<1 cm) and non-tender nodes. There was enlargement of the spleen. The body temperature was 37.0 °C. The remainder of the examination was unremarkable.

Laboratory investigations revealed: erythrocyte sedimentation rate 83 mm/U (0 to 20 mm/U), haemoglobin 6.3 mmol/l (7.5 to 10 mmol/l), mean corpuscular volume 86 fl (80 to 100 fl), white blood cells normal, platelets 36 x 10^9/l (150 to 400 x 10^9/l), creatinine 75 µmol/l (65 to 95 µmol/l), and lactate dehydrogenase 216 U/l (0 to 247 U/l). Virus serology including Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus was negative.

An FDG-PET scan showed pathological FDG accumulation in multiple lymph nodes both above and below the diaphragm, and splenomegaly with diffusely increased FDG accumulation (*figure 1*). In addition, a lymph node was excised (*figure 2*).

Figure 1. *PET scan showing pathological FDG accumulation in multiple lymph nodes both above and below the diaphragm, and splenomegaly with diffuse increase of FDG accumulation*

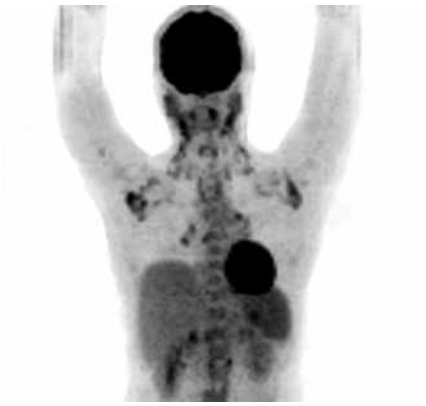
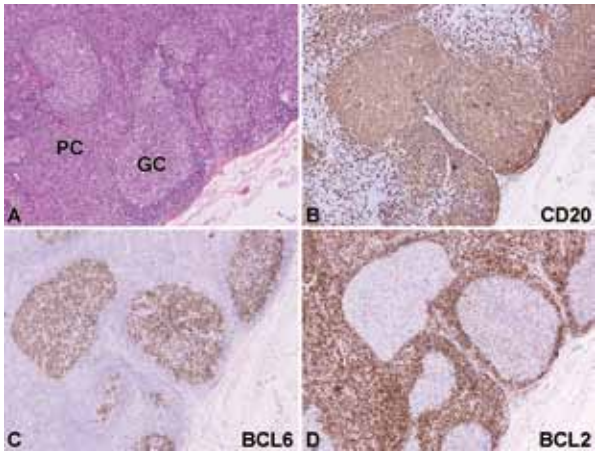


Figure 2. *Histological examination of lymph node biopsy.*



PC = paracortex; GC = germinal centre.
(A) Detail of a lymph node showing follicular hyperplasia and expansion of the paracortical zone. Haematoxylin and eosin stain. (B)-(D) Immunohistochemistry demonstrating the non-neoplastic nature of the lymph node. (B) B-lymphocytes showing membrane expression of CD20. (C) Germinal centre B-lymphocytes showing nuclear expression of the germinal-centre specific transcription factor protein BCL-6. (D) T- and B-lymphocytes showing cytoplasmic expression of the antiapoptotic protein BCL-2. Germinal centre B cells typically lack BCL-2 expression. Magnification x 40.

WHAT IS YOUR DIAGNOSIS?

See page 288 for the answer to this photo quiz.

PHOTOQUIZ

An unusual cause of a usual presentation

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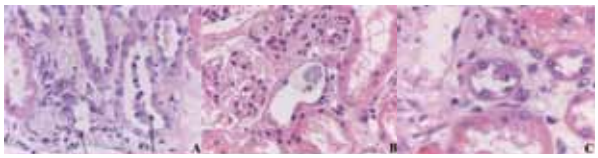
A 61-year-old HIV-positive male presented at the clinic complaining of a fever and extreme tiredness for a week. Additional complaints were myalgia, headache and macroscopic haematuria. On physical examination the patient was ill, with a temperature of 40 °C, blood pressure of 135/84 mmHg, pulse rate of 82/min and the patient had bilateral flank tenderness. The patient's medical history reveals a well regulated HIV status with an undetectable viral load and a repeated deep venous thrombosis necessitating lifelong anticoagulation. The antiretroviral therapy consists out of a combination therapy of abacavir, lamivudine, and zidovudine.

Table 1. *Laboratory results with patients normal test values, results at first presentation and results at the second presentation*

		'Last known'	1st presentation	2nd presentation
Haemoglobin	g/l	8.8	10.8	6.8
Leucocytes	x 10^9/l	6.2	18.2	14.7
Thrombocytes	x 10^9/l	306	137	327
ESR	mm/hr		24	89
CRP	mg/l		54	113
Creatinine	µmol/l	88	850	122
BUN	mmol/l	2.8	31.8	6.1
Sodium	mmol/l	138	126	136
Potassium	mmol/l	4.6	4.8	4.2
CD4	x 10^9/l	1,23	1,18	
ANCA ANA Anti-GBM		Negative Negative Negative		

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BUN = blood urea nitrogen; ANCA = antineutrophil cytoplasmic antibodies; ANA = antinuclear-antibody; Anti-GBM = antiglomerular basal membrane.

Figure 1. *Tubular lesions: The biopsy shows a patchy tubulo-interstitial lymphocytic infiltrate, but no tubulitis*



(A) Pleomorphic tubular epithelial cells with enlarged nuclei (black arrow). Sludging of necrotic epithelial cells in the tubular lumen (open arrow). (B) Cristallyne matter in tubular lumen. (C) Mitotis of tubular epithelial cells, indicative of epithelial repair in acute tubular necrosis

The patient had not been abroad, but had recently visited his holiday home in the eastern part of the Netherlands. Blood results are listed in *table 1*. Urinalysis showed proteinuria and haematuria. Empirical treatment with antibiotics was started after obtaining blood cultures. Although fever and other physical complaints resolved after a few days, renal function further deteriorated. To rule out a vasculitis, a kidney biopsy was performed, which demonstrated a nonspecific tubulo-interstitial lymphocytic inflammation and tubular necrosis, without evidence of glomerular disease (*figure 1*).

Within a few days the renal function improved spontaneously and the patient was discharged; there was no need to initiate renal replacement therapy. Several days later he visited the outpatient clinic with recurrent high fever and malaise. Second presentation laboratory test results are also listed in *table 1*.

WHAT IS YOUR DIAGNOSIS?

See page 289 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

Multifocal adrenal nerve tissue?

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A 52-year-old female was referred to our outpatient clinic with a right-sided adrenal incidentaloma. Her medical history was unremarkable besides a well-regulated hypertension for ten years. She stopped smoking 12 years ago. Evaluation in another hospital for macroscopic haematuria with a CT scan revealed a right-sided adrenal mass of 8 cm which compressed the inferior vena cava without signs of vasoinvasive disease. Furthermore, two enlarged para-aortic lymph nodes with a diameter of 3 cm were identified (*figure 1*).

She did not complain of abdominal pain or discomfort. In addition, there were no signs of weight loss, catecholamine or cortisol excess. Physical examination showed no cushingoid features and a body mass index of 40 kg/m^2.

Figure 1. *Right-sided adrenal mass of 80 mm. In the para-aortic region an enlarged lymphnode is visible (diameter 28 mm).*

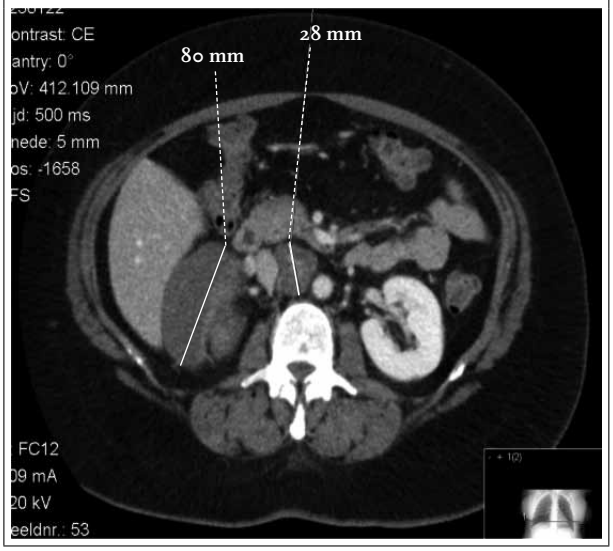
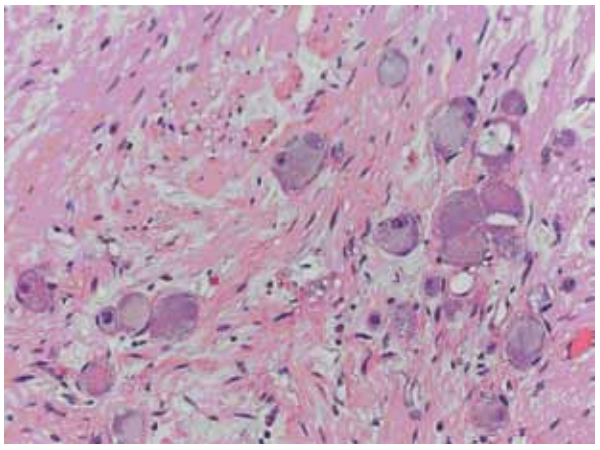


Figure 2. *In the upper left corner neuronal cells. In the middle a group of larger ganglioncells, with in the middle a ganglion cell with a double nucleus, typical for ganglioneuroma.*



Blood pressure was 145/85 mmHg. Breath sounds were normal and no lymphadenopathy was noticed, nor were there any palpable abnormalities of the breasts indicative of carcinoma.

Biochemical evaluation, including 24-hour urinary excretion of catecholamines, cortisol and a dexamethasone suppression test, was normal. Additional mammography and CT scanning of the thorax showed no abnormalities. Since the clinical presentation was suspicious for metastatic disease of an unknown primary tumour a CT-guided biopsy was performed. An admixture of neuronal tissue and ganglion cells was seen (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 290 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

A bulky mass in an HIV-positive patient

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A 44-year-old man with human immunodeficiency virus (HIV) infection was referred to Tygerberg Academic Hospital (Cape Town, South Africa) with a two-month history of progressive swelling of the left side of his face, difficulty swallowing, fever, night sweats, and involuntary weight loss of 7 kg. He had been on treatment for pulmonary tuberculosis for four months. On physical examination he had a large mass on his left cheek and swelling of the ipsilateral eyelid, both lips, and his tongue (*figure 1*). The CD4 count was 98 cells per cubic mm.

Figure 1. *Patient on presentation*

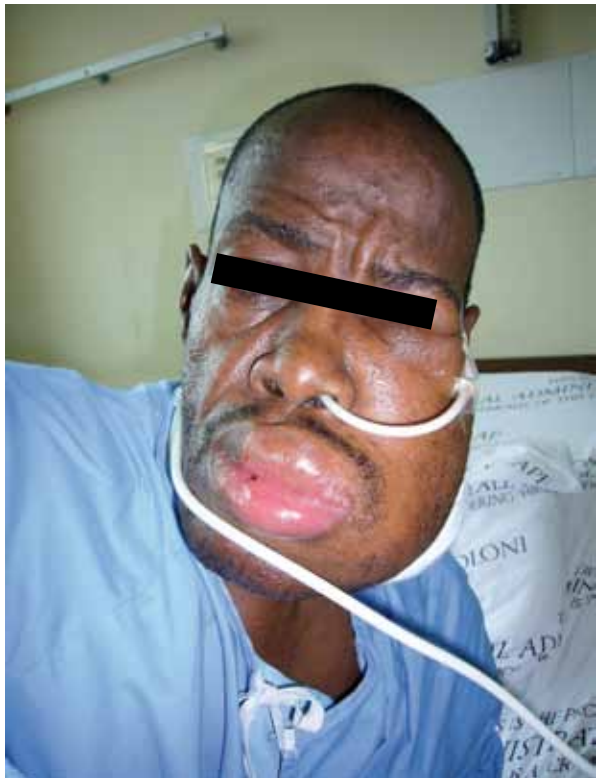
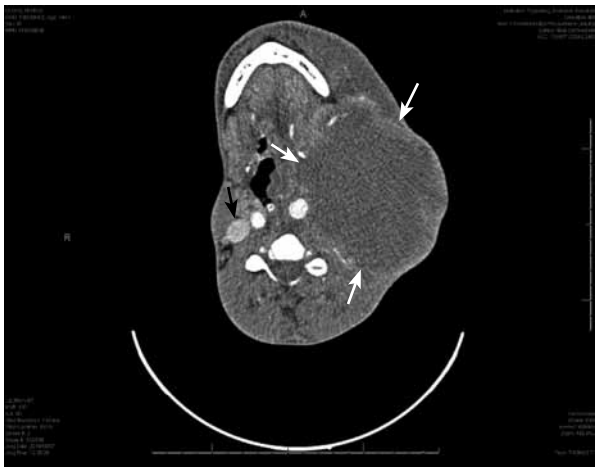


Figure 2. *CT-scan of the neck. White arrows point to the mass; black arrow points to the right internal jugular vein; note that left internal jugular vein is not visible.*



Contrasted computed tomography (CT) scanning showed a ring enhancing mass extending from the infratemporal fossa to the submandibular region with occlusion of the left internal jugular vein and displacement of the midline to the right (*figure 2*). Alongside with extensive lymphadenopathy on both sides of the diaphragm, bilateral lung and kidney nodules, and hepatosplenomegaly. Previous fine needle aspirations of the mass on his cheek had twice given inconclusive results. A nasopharyngeal biopsy was taken for histological examination.

WHAT IS YOUR DIAGNOSIS?

See page 291 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 284)

A YOUNG WOMAN WITH GENERALISED LYMPHADENOPATHY

When the history taking was repeated the patient stated she had photosensitivity. Additional laboratory findings revealed: direct Coombs reaction 3+, positive antinuclear antibody, positive antidouble stranded DNA and active urinary sediment (microalbumin/creatinine ratio 96.55 mg/mmol, erythrocytes 92 /ul, leucocytes 14 /ul). The lymph node revealed a *reactive lymphadenopathy*, without signs of malignancy. In the lymph node, neither immunophenotyping nor B cell receptor gene rearrangement analysis could demonstrate a clonal B cell proliferation.

Altogether, SLE was diagnosed based on the following criteria: photosensitivity, haematological and renal disorders, and positive serological testing. Extensive lymphadenopathy, as seen in this case, is a rare first presentation of SLE.[1]

In the evaluation of Hodgkin's and non-Hodgkin's lymphoma (NHL) a PET scan with 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) has been used as a valuable diagnostic tool. In contrast, in SLE, FDG-PET has so far solely been used in the evaluation of central nervous system involvement.[2] FDG uptake is not tumour specific for malignancies because inflammatory lesions can also concentrate the tracer, including infectious diseases, inflammatory conditions such as vasculitis and arthritis, and granulomatous diseases such as tuberculosis and sarcoidosis.[3] Our case shows that it is important for a physician to always keep an open eye for an alternative diagnosis. The more widespread use of FDG-PET scanning may more often lead to the suspicion of lymphoma in benign conditions such as autoimmune diseases.

Histopathology remains the golden standard method for the diagnosis and classification of persistently enlarged lymph nodes. In SLE, the lesion is characterised by varying degrees of coagulative necrosis with haematoxylin bodies or reactive hyperplasia.[4]

In summary, SLE can present with extensive lymphadenopathy. Furthermore, the pattern of FDG uptake on a PET scan in SLE can mimic lymphoma. Being aware of the similarities between SLE and lymphoma is of the utmost importance for making the correct diagnosis.

ACKNOWLEDGEMENTS

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ANSWER TO PHOTO QUIZ (PAGE 285)

AN UNUSUAL CAUSE OF A USUAL PRESENTATION

Hantaviruses, a group of single-stranded RNA viruses of the *Bunyaviridae* family, are an important cause of severe disease around the world.[1] Depending on the sub-type of the virus, clinical manifestations may vary enormously. In the Netherlands the hantavirus sub-type *Puumala* causes a disease called nephropatia epidemica. Infection with a hantavirus can take place through the inhalation of virus containing aerosol from rodent excreta, mainly the *Myodes glareolus* in the Netherlands, whose natural habitat is in forested areas. The incubation time is around 2 to 3 weeks followed by a febrile period. After the febrile period four stadia can be recognised: a hypotensive, oliguric, diuretic and a convalescent period.[1] Environmental- and occupation-related factors can increase the risk of infection with a hantavirus.[2] In the Netherlands the number of confirmed hantavirus infections is limited, possibly due to unawareness and under-recognition. As the incidence is highest in the eastern parts of the Netherlands, hantavirus should be part of the differential diagnosis in patients presenting with fever and renal failure, either living or have recently visited this region.[2] The patient described in this paper had stayed at his holiday home in Twente 3.5 weeks prior to the start of his complaints. During this stay he had cleaned his barn where he probably inhaled the fumes of mice excrement. The suspicion of a hantavirus infection may be confirmed with serology or PCR. In the Netherlands these tests are available at the National Institute of Public Health and the Environment (RIVM) and the Erasmus Medical Centre. As in this case, renal failure in nephropathia epidemica is usually completely reversible and only 1% of cases require temporary dialysis.[3] While treatment of hantavirus infection primarily consists of supportive care, early diagnosis of the infection can significantly reduce the duration of any necessary hospital stay and the possible inappropriate use of antibiotics.[4]

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ANSWER TO PHOTO QUIZ (PAGE 286)
MULTIFOCAL ADRENAL NERVE TISSUE?

The biopsy raised the possibility of adrenal ganglioneuroma. Since malignant transformation of ganglioneuromas into peripheral nerve sheath tumours has been described and considering the para-aortic lymph nodes, malignancy could not be excluded completely. A laparotomy was performed and an adrenal mass of 10 cm and two lymph nodes of 2 and 7 cm in diameter, were removed. Pathological examination confirmed the earlier suggested diagnosis of ganglioneuroma of the adrenal gland. The suspected lymph nodes, appeared to be ganglioneuroma foci.

Ganglioneuromas are rare benign tumours originating from the neural crest, specifically the sympathetic ganglion cells; they sometimes develop from chemotherapeutically treated neuroblastomas.[1-4] Neural crest cells are highly differentiated and do not contain mitotic features making them hormonally inactive. However, catecholamine hypersecretion has been reported in up to 20 to 39% of cases. In 40 to 71% ganglioneuromas occur as a composite tumour with pheochromocytoma.[1-6] Pheochromocytomas also arise from the neural crest from parasympathetic cells. When ganglioneuroma is found in combination with a pheochromocytoma, testing for the known genes associated with pheochromocytoma (SD related mutations, NF1, VHL and RET mutations) is advised.

Ganglioneuroma predominantly appear in the posterior mediastinum and retroperitoneum. Approximately 10% develop in the head and neck region.[7-9] Adrenal ganglioneuromas comprise 50% of the retroperitoneal ganglioneuromas and arise from the medulla in 20 to 30% of cases.

Multifocal presentation as seen in this case is rare and is sometimes seen in neurofibromatosis type 1. Ganglioneuromas have a very good prognosis after resection, even when resection has been incomplete.[9,10] This case illustrates that a large adrenal mass with para-aortic lymphadenopathy is not always pathognomonic for metastatic disease with a cumbersome clinical course, but that a rare benign tumour such as ganglioneuroma could be included in the differential diagnosis.

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ANSWER TO PHOTO QUIZ (PAGE 287)

A BULKY MASS IN AN HIV-POSITIVE PATIENT

DIAGNOSIS

The biopsy showed malignant lymphoid cells just below the nasopharyngeal mucosa. The morphological and immunohistochemical profile confirmed the presence of a diffuse large B-cell lymphoma. Bone marrow and cerebrospinal fluid examination were unremarkable. In the absence of rituximab, the patient was treated with a chemotherapeutic regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), together with highly active antiretroviral therapy (HAART) consisting of lamivudine, tenofovir disoproxil fumarate and efavirenz and prophylactic trimethoprim-sulfamethoxazole. He died of sepsis after three courses of chemotherapy, during an episode of neutropenia. Forty percent of HIV-infected individuals will develop a form of cancer during their lives.[1] The risk of developing a non-Hodgkin's lymphoma (NHL) in patients with acquired immunodeficiency syndrome (AIDS) is 165-fold increased, compared with the population not infected with HIV. These tend to be more high-grade malignancies and have more extranodal and central nervous system involvement.[2] Pathophysiology of NHL in HIV-infected patients is complex and heterogeneous. Dysregulation of the immune system by HIV, leading to loss of control of Epstein-Barr virus (EBV) infection, seems to play an important role.[3] Targeting the CD20 antigen on B-lymphocytes with the monoclonal antibody rituximab added to the CHOP regimen, has led to a better outcome in patients with B-cell malignancies.[4] Treatment outcomes have also improved considerably since the addition of HAART to chemotherapy, leading to outcomes comparable with HIV-uninfected individuals. Advanced immunodeficiency and high age are associated with worse outcomes, highlighting the need for early diagnosis of both HIV infection and lymphoma to improve patient survival.[5] We advocate to test for HIV in every patient who presents with a malignant lymphoma. Secondly, every known HIV-infected individual with unexplained nodules should be accurately worked up for the presence of a malignancy.

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SPECIAL ARTICLE

The effects of implementation of the Surviving Sepsis Campaign in the Netherlands

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ABSTRACT

To reduce unintentional and avoidable adverse events in patients in hospitals in the Netherlands, a patient safety agency (VMS) programme was launched in 2008. Among the VMS topics, the programme 'optimal therapy in severe sepsis', according to the international Surviving Sepsis Campaign (SSC), aims to improve early diagnosis and treatment of sepsis to reduce sepsis mortality by 15% before the end of 2012.

We analysed compliance data submitted to the international SSC database from the Netherlands and compared these data with published international SSC results.

Data of 863 patients, representing 6% of the international data (n=14,209), were used for analysis. In the Netherlands, the resuscitation bundle compliance improved significantly from 7% at baseline to 27% after two years (p=0.002). Internationally, the resuscitation bundle compliance increased significantly from 11 to 31% (p<0.001). In contrast with the international results (18% baseline, 36% after two years), the compliance with the management bundle did not improve (24% baseline, 25% after two years). At baseline, hospital mortality was significantly higher compared with internationally (52 *vs* 37%; p=0.03) and decreased significantly from 52% at baseline to 35% after two years (p=0.049). In the Netherlands, the decrease in mortality was significantly more pronounced after implementation of the SSC (p<0.001).

In the Netherlands, following implementation of the SCC guidelines, compliance with the resuscitation bundle increased significantly, while compliance with the management bundle remained unaffected. This was associated with a significant improvement in hospital survival. In view of the VMS programme and goals, further implementation of the SSC is warranted.

KEYWORDS

Compliance, implementation, management bundle, resuscitation bundle, Surviving Sepsis Campaign

INTRODUCTION

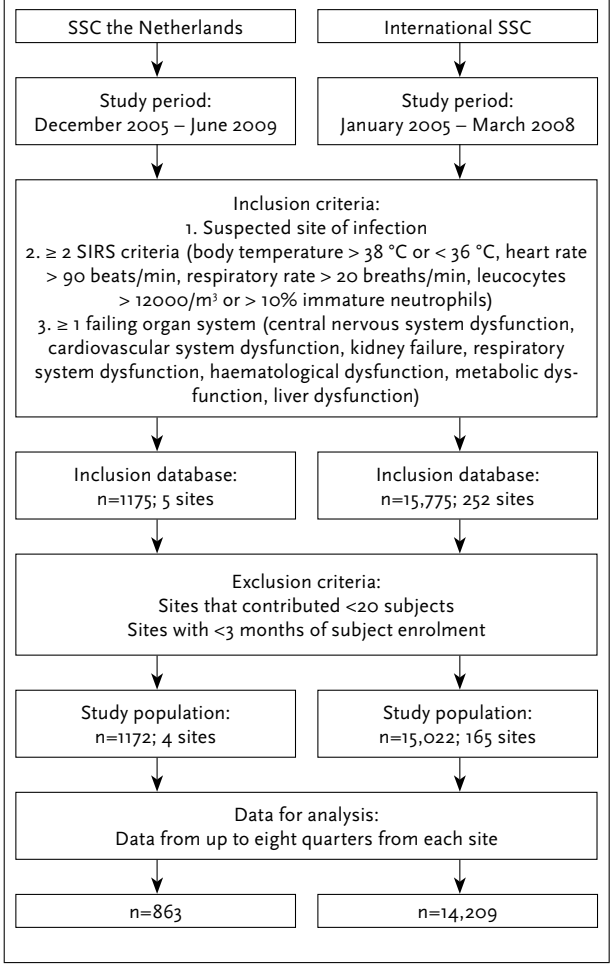
In the Netherlands, it is estimated that 15,500 patients with severe sepsis and 6000 patients suffering from septic shock are annually admitted to an intensive care unit (ICU).[1] With a mortality rate of 30 to 50% severe sepsis/septic shock is the most important cause of death in non-cardiac ICU patients.[2] To provide better guidelines to improve early diagnosis and treatment of severe sepsis and to reduce its mortality, the Surviving Sepsis Campaign (SSC) was launched in 2002.[3,4] The most important SSC guideline recommendations are summarised into two bundles: the resuscitation bundle (six elements to start immediately and to be completed within six hours) and the management bundle (four elements to be completed within 24 hours), published in 2004.[3,5] Since then, the sepsis bundles have been adopted in ICUs,[6-8] emergency departments,[9-11] and nursing wards.[12-18]

In the Netherlands, a national committee and SSC website was established facilitating the possibilities to report bundle compliance and patient outcome to the international database. In addition, the Dutch Association of Hospitals (NVZ), Dutch Federation of University Medical Centres (NFU), Order of Medical Specialists (Order), National Expert Centre for Nursing (LEVV), and the Association for Nurses in the Netherlands (V&VN) initiated the National Patient Safety Agency (VMS: www.vmszorg.nl). VMS aims to reduce the unintentional and avoidable damage in patients in Dutch hospitals by 50% by December 2012. Among other VMS topics, the early diagnosis and treatment of patients with severe sepsis are specific guideline items. The goal of the VMS is to increase compliance with the resuscitation bundle and management bundle elements to an average of 80% and to reduce both the in-hospital mortality and the mortality within 30 days after the diagnosis of severe sepsis by 15% compared with mortality data from 2007.

Recently, the results of the international guideline-based performance programme were published.[12] Patient data and bundle performance data of 14,209 patients from 165 sites worldwide demonstrated that compliance with the SSC bundles was associated with continuous quality improvement in sepsis care and a sustained decrease in mortality.

The aim of our present study was to analyse the data submitted by hospitals in the Netherlands and to compare these results with the international SSC results.

Figure 1. *Study population: SSC database the Netherlands and the international SSC database*



MATERIALS AND METHODS

Study design and population

Patient data and bundle compliance data were collected from December 2005 to June 2009. Inclusion criteria were adult patients (>18 years) admitted to emergency departments, clinical wards, and ICUs with a suspected or proven infection, ≥2 systematic inflammatory response syndrome (SIRS) criteria, and ≥1 failing organ system.[11,18] Participating sites that included ≤20 patients and sites with <3 months of patient enrolment were excluded for this study (*figure 1*).

The global SSC improvement initiative was reviewed and approved by the Cooper University Hospital Institution Review Board. As patient data were obtained anonymously and no patient-related interventions were carried out, no additional approval from an Ethics Committee was necessary.

Data collection and variables

The database used for this study was part of the international SSC database.[12] The relevant patient characteristics included department of admission (from emergency department, from other unit or ICU with other diagnosis), site of infection, diagnosis, and hospital mortality (*table 1*). In accordance to country-specific privacy laws, patient age and gender were not collected in the international SSC database and were therefore also not available for our study.

Performance data of the six resuscitation bundle elements and performance data of the four management bundle elements were collected (*table 2*). The bundle element 'drotrecogin alfa policy' implies that each hospital has formulated its own drotrecogin alfa policy. If the policy is to treat patients with drotrecogin alfa, a patient that did not receive the drug is classified as not compliant. If the policy is not to administer drotrecogin alfa, and the drug is not given, this is viewed as compliant to the local policy. If no formal policy is present, the patients that fulfil the criteria but did not receive the drug are scored as not compliant.

All data were organised by quarter, with the first three months that a site entered patient data into the database

Table 1. *Patient characteristics: the Netherlands versus international*[12]

	Subjects, % the Netherlands (n = 1172)	Subjects, % International (n = 15,022)	P-value*
Admission			
From emergency department	28.2	52.4	<0.001
From other unit	57.8	34.8	<0.001
ICU with other diagnosis	14.1	12.8	-
Diagnosis			
Severe sepsis	24.1	28.5	0.001
Septic shock	75.9	71.5	0.001
Site of infection			
Pneumonia	47.2	44.4	-
Urinary tract infection	9.3	20.8	<0.001
Abdominal	36.5	21.1	<0.001
Meningitis	1.8	1.6	-
Skin	3.6	5.9	0.001
Bone	1.0	1.2	-
Wound	5.0	3.8	0.04
Catheter	3.7	4.1	-
Endocarditis	1.7	1.1	-
Device	1.0	1.1	-
Other infection	5.9	12.7	<0.001

*** Significant differences between patient characteristics from the Netherlands and the international patient characteristics (<0.05)**
ICU; intensive care unit

defined as the first quarter, regardless of when those months occurred. Data from up to eight quarters from each site were used to analyse bundle compliances (*figure 1*). Furthermore, data from the initial quarter (first quarter of data submission from each institution during the two-year data analysis period) and the final quarter (the last quarter of data submission from each institution during the two-year data analysis period) were used to compare changes in compliance with the bundle elements between the initial quarter and the final quarter and to compare the data from the Netherlands with the international data.

Outcome measures

The primary outcome measure was change in compliance with the entire resuscitation bundle and management bundle, and change in the completion of the ten individual bundle elements. We included hospital mortality rate as secondary outcome measure.

Statistical analysis

Data are presented as percentages, odds ratios (ORs) with 95% confidence intervals (95% CI). To analyse the differences in compliance rates between the quarters, both overall and for each of the ten separate elements, we used the Chi-square test. In a similar way, we analysed the differences in compliance rates between the Netherlands and the international results. Due to the relatively small number of patients from the Netherlands, the Fisher's exact test was used to analyse the differences between bundle compliance in the initial quarter compared with the final quarter. To determine the effect of the SSC on the compliance rate of the bundles over the study period we used linear regression analysis. To analyse the impact of compliance with the individual bundle elements, a multivariate logistic regression analysis was performed. A two-tailed p value below 0.05 was considered statistically significant. Data were analysed using SPSS 16.01 (SPSS, Chicago, IL) and Graph Pad V 5.0 (Graph pad Prism software).

Table 2. *Compliance with the resuscitation and management bundle elements in the Netherlands: percentages per quarter (n = 863)*

	Q 1[a] n=62	Q 2[a] n=97	Q 3[a] n=128	Q 4[a] n=117	Q 5[a] n=139	Q 6[a] n=127	Q 7[a] n=93	Q 8[a] n=100
Resuscitation bundle (n)								
1. Measure lactate (863)	71	77	69	76	75	79	86	79
2. Blood cultures before antibiotics (863)	60	52	58	66	58	63	56	70
3. Broad-spectrum antibiotics (863)	50	59	48	47	51	56	50	54
4. Fluids and vasopressors (785)	86	90	80	77	83	81	90	79
5. CVP >8 mmHg (633)	45	55	55	39	50	54	58	58
6. ScvO2 >70% (629)	8	24	25	24	45	37	38	49
Completion of all resuscitation bundle elements (863)	7	12	13	15	18	21	19	27
Management bundle (n)								
1. Steroid policy (628)	63	82	75	77	73	81	86	91
2. Drotrecogin alfa policy followed (863)	73	62	54	50	46	60	57	72
3. Glucose control (863)	50	50	53	53	61	56	59	47
4. Plateau pressure control (634)	88	80	77	78	75	77	83	84
Completion of all management bundle elements (863)	24	17	20	16	17	26	22	25

[a]**Represents each quarter of data submission from each institution during the two-year data analysis period, regardless of total number of each institutions participation.**

RESULTS

Nationwide, 1172 patients from four different general hospitals were included in the SSC database (*figure 1*). Internationally, 15,022 patients from 165 different sites were included. In contrast to the international data, where patients were most likely admitted to the ICU through the emergency department, most patients came to the ICU from the general nursing ward in the Netherlands. Furthermore, significantly more septic shock patients were included (p=0.001) and the sites of infection were not comparable with the international data (*table 1*).

Since analysis of the bundle compliance was limited to the first two years of patient inclusion at each site, the compliance data of 863 patients, representing 6% of the international analysed data, were used for further analysis. For the international bundle compliance analysis, data of 14,209 patients were available (*figure 1*).

CHANGE IN BUNDLE COMPLIANCE

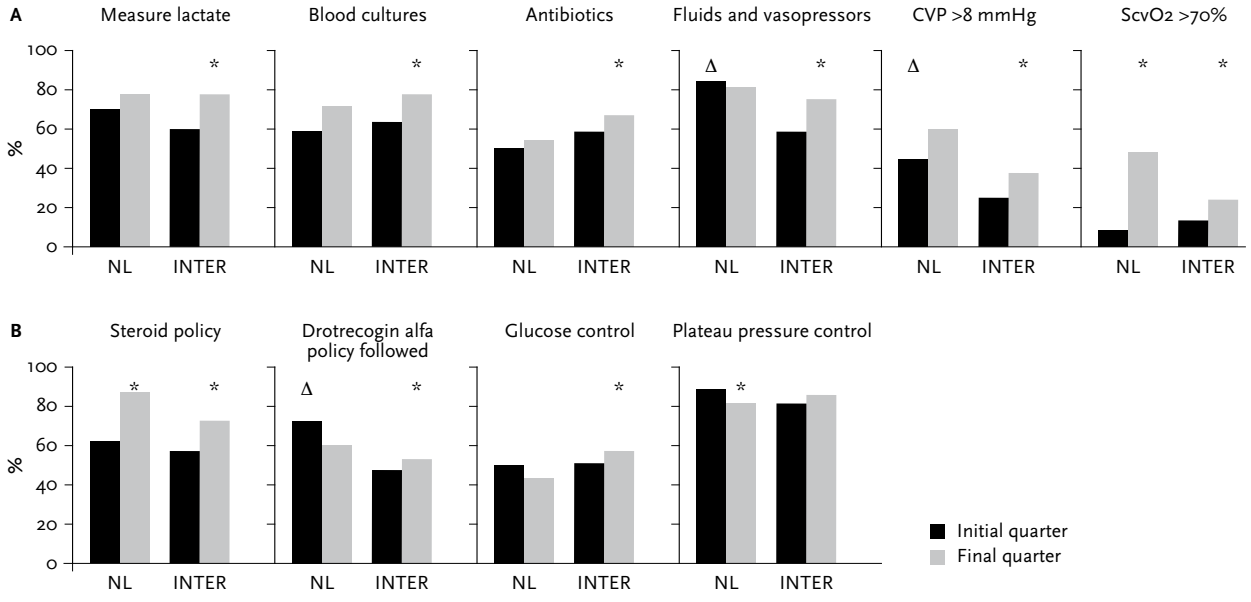
The compliance with the complete bundles and the individual bundle elements by quarter during two years in the Netherlands are represented in *table 2*. During the first quarter, the compliance rate with the resuscitation bundle and management bundle was 7% and 24% respectively, compared with 11% and 18% internationally.[12]

Although in the initial quarter no significant differences in the overall bundle compliance rate between the Netherlands and the international bundle compliance rate were found (resuscitation bundle p=0.27; management bundle p=0.25), the compliance with three individual bundle elements ('administration of fluids and vasopressors', 'achieving a CVP >8 mmHg', and 'drotrecogin alfa policy followed') was significantly higher (p<0.001) in the first quarter in the Netherlands (*figure 2*).

In the Netherlands, the compliance rate with the complete resuscitation bundle improved significantly to 27% (*p*=0.002) by the end of two years, and statistically significant improvement was achieved by the fifth quarter (*figure 3A*). Internationally, the compliance with the resuscitation bundle increased to 31% by the end of two years, achieving statistical significance (p<0.0001) by the second quarter (*figure 3A*). For the management bundle no statistically significant differences in compliance rates between baseline and the end of two years were found in the Netherlands (*figure 3B*), while internationally, the compliance with the management bundle significantly increased from 18 to 36% by the end of two years.[12]

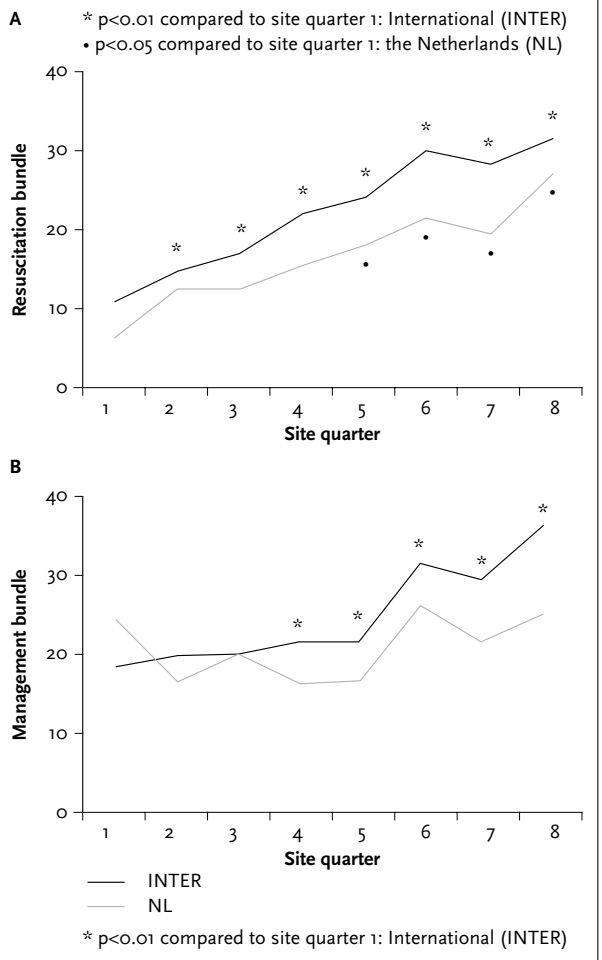
Changes in compliance with the individual bundle elements between the initial quarter and the final quarter are presented in *figure 2*. In the final quarter, a significant improvement in the completion of the individual resuscitation bundle element '$ScvO_2$ >70%'

Figure 2. *Change in compliance with the individual bundle elements in the initial quarter and the final quarter: results from the Netherlands versus the international results*[12]



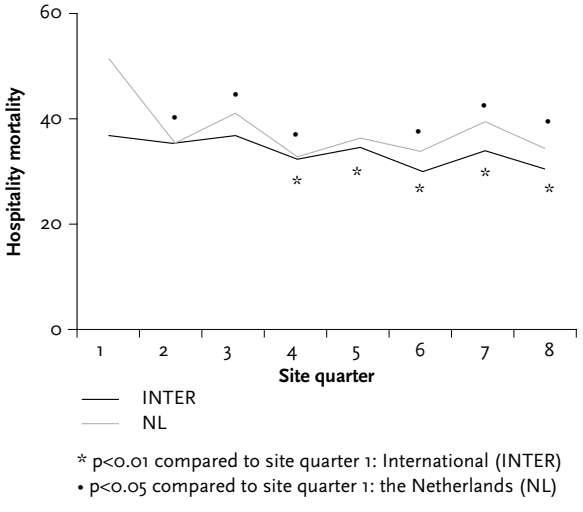
Δ Significant differences between initial quarter the Netherlands (NL) and initial quarter international (INTER).
*** Significant differences between initial quarter and final quarter.**
A, Compliance with the resuscitation bundle elements; B, Compliance with the management bundle elements.

Figure 3. *Change in bundle compliance per quarter over two years of data collection.*



A, Compliance with the complete resuscitation bundle; B, Compliance with the complete management bundle.
Results from the Netherlands (n=863) versus the international results (n=14,209)[12]

Figure 4. *Change in hospital mortality per quarter over two years of data collection.*



Results from the Netherlands (n=863) versus the international results (n=14,209)[12]

(8 to 48%; *figure 2A*), and the management bundle element 'steroid policy' (63 to 88%; *figure 2B*) was attained in the Netherlands. Internationally, the completion of all six resuscitation bundle elements and three out of four management bundle elements improved significantly.[12]

HOSPITAL MORTALITY

Data from the Netherlands showed that the hospital mortality at baseline was 52% and significantly decreased by the end of two years to 35% (p<0.05). Internationally, the baseline hospital mortality was 37% and significantly decreased to 31% (*figure 4*).[12] The hospital mortality at baseline was significantly higher in the Netherlands compared with the international hospital mortality (52 *vs* 37%; p=0.03) and the decrease in hospital mortality in the Netherlands was significantly more pronounced than the achieved decrease in hospital mortality in the international database: 17 *vs* 6% (p<0.001).

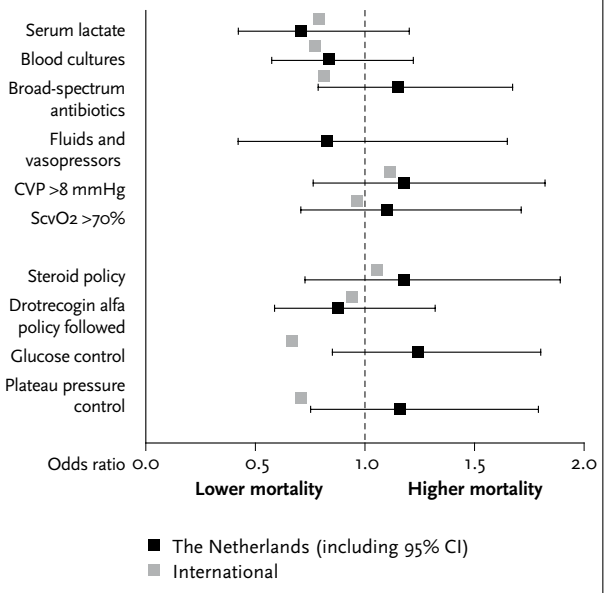
The impact of the individual bundle elements on the unadjusted hospital mortality is represented in *figure 5*. In the Netherlands, the performance of four out of ten bundle elements contributed to a lower hospital mortality, whereas seven out of nine bundle elements contributed to a lower mortality internationally (the impact of the tenth bundle element 'fluids and vasopressors' on hospital mortality was not known). The beneficial impact of 'glucose control' and 'plateau pressure control' found internationally, was not confirmed in the data from the Netherlands as the 95% CIs do not include the international data point.

Independent of changes in time, of all patients who were treated in the Netherlands in compliance with the resuscitation bundle, mortality was borderline significantly lower (31 *vs* 39%, p=0.057) compared with the patients who were not.

DISCUSSION

The main finding of our study is that in the included hospitals in the Netherlands the compliance with the resuscitation bundle significantly improved by implementation of the SSC while, in contrast with the international results, the compliance with the management bundle did not improve. The hospital mortality decreased significantly after implementation of the SSC and compared with the international data, the

Figure 5. *Impact of the individual bundle elements on the unadjusted hospital mortality.*



Results from the Netherlands (n=863) versus the international results (n=14,209)[12]

hospital mortality in the Netherlands was significantly higher at baseline and decreased significantly more after implementation of the SSC.

Although the results of the implementation of the SSC bundles have been reported in several studies,[7,8,15,17] we feel it is of importance to report the compliance rates and outcome results of patients in the Netherlands. Our data demonstrate and confirm that focus on the SSC guidelines can improve the care of patients with sepsis in the Netherlands, and that indeed this is associated with a better survival for sepsis patients. Importantly, our study does not describe the effect of implementation of the SSC bundles in all hospitals and data were only collected until June 2009. Since then, it seems likely that the SSC bundles are implemented in more Dutch hospitals and the bundle compliance further improved because of the performance of several local and national implementation programmes related to the VMS safety programme.

While the compliance with the resuscitation bundle improved significantly, compliance with the management bundle did not. The management bundle consists of therapies with proven efficacy in patients in the ICU.[3] The lack of improvement in therapies given in the ICU is a striking finding, especially since mainly intensivists are involved in the implementation efforts of the SSC guidelines. Therefore, the implementation of these therapies needs further attention.

Overall, and possibly against general belief, the complete adherence to the bundles was poor at baseline. Despite the implementation of the SSC bundles, the completion of all resuscitation bundle elements as well as all management bundle elements occurred only in approximately a quarter of all patients with severe sepsis and septic shock following implementation. Nevertheless, these results are comparable with international results.[6,7,12,20] In Spain, the implementation of the SSC bundles in 59 medical-surgical ICUs was associated with improved guideline compliance and lower hospital mortality. Compliance with the resuscitation bundle was only 13% at postintervention and 7% during long-term follow-up. Compliance with the management bundle was 20% at postintervention and 27% during long-term follow-up.[20] In other studies compliance varies from 4%[6] to 52%.[21] So far, the cost-effectiveness of the implementation of the SSC bundles in the Netherlands is not known. In Spain, a significant reduction in mortality resulted in an increase in costs per patient of only € 1736, mainly attributable to the increased length of stay.[22]

Several limitations of this study need to be addressed. At baseline, mortality was higher in patients in the Netherlands compared with the international database. Because of the significant differences in case mix (including a higher proportion of patients with septic shock, admitted from the ward, and differences in the site of infection) the relevance of this baseline difference in mortality is not clear. Since we had no access to individual patient data in the international database, adjustments could not be made. In addition, the methods used in other studies are not comparable with the methods used in our study and therefore it is not possible to benchmark the results from the Netherlands with the results from a country with a similar high baseline mortality.
Nevertheless, the increase in bundle compliance associated with an improvement in mortality is paramount and in accordance with earlier studies.[7,8,12-14,20-25] The fact that most patients in the Netherlands came from the ward, while most international patients were admitted to the ICU by the emergency department, may be relevant for the initiation of the resuscitation bundle, as sepsis patients are more likely to be treated within the time frames of the SSC bundles than ward patients. For example emergency department nurses can play a vital role in recognising and managing patients with severe sepsis.[11]

Although the literature provides a large number of different strategies to implement innovations such as the SSC bundles, e.g., educational meetings, reminders, and feedback, not one of these implementation strategies seems to be superior to the other and most show mixed results.[9-11,15,26,27] Due to the relatively small number of included patients and different implementation strategies

per hospital, we were unable to evaluate the effects of the applied implementation techniques on bundle compliance. Furthermore, the expanded attention to severe sepsis and septic shock, changes in hospital practice, changes on the level of the organisation, or not SSC related implementation techniques may (also) have contributed to the changes in bundle compliance. Therefore, it is not possible to conclude which factors were (to what degree) responsible for the achieved improvement.

In conclusion, implementation of the SSC bundles and the compliance registration improved insight into the current quality of care for patients with severe sepsis and septic shock. Comparable with other regions of the world, there is room for improvement in the treatment of these patients in the Netherlands. Both national and international improvements in SSC compliance were associated with sustained, continuous quality improvement in sepsis care and better outcome of septic patients, although in an observational study a cause-effect relationship cannot be established. Especially the lack of improvement of the compliance with the management bundle needs further attention. To achieve a higher SSC bundle compliance and better patient outcome in the Netherlands, sepsis education, repeated evaluation of the SSC bundle compliance, and participation in the VMS safety programme is necessary.

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INFORMATION FOR AUTHORS

Aims and scope

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Acknowledgement: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.