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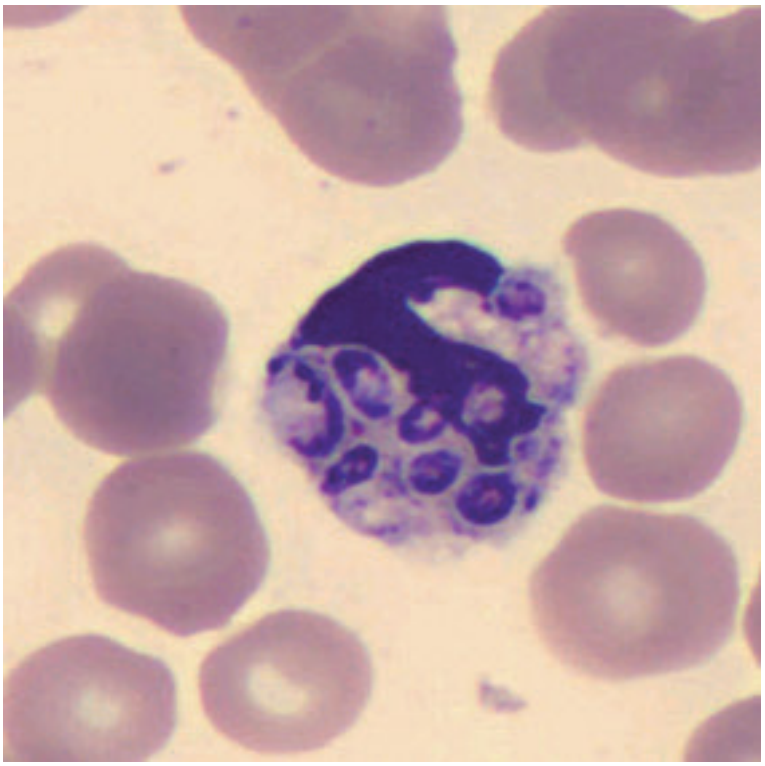

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July 2014, Vol. 72, No. 06, Issn 0300-2977

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EDITORIAL

Searching for balance in old age: about water and salt

F.U.S. Mattace-Raso

Department of Internal Medicine, Division of Geriatrics, Erasmus University Medical Center Rotterdam, the Netherlands, tel. +31(0)10-7035979, e-mail: f.mattaceraso@erasmusmc.nl

Hyponatraemia (defined as a serum sodium level < 135 mml/l) is the most frequent serum electrolyte disorder in clinical practice. Older adults are particularly prone to develop hyponatraemia, due to comorbidities and consequent frequent use of medication and to age-related changes in water and electrolyte balance. Moreover, serum sodium concentrations can slightly decrease with age; a slight reduction in serum sodium concentration equal to 1 mmol/l /decade has been documented.

Hyponatraemia is frequent in older adults. Previous studies performed in both the acute hospital setting and chronic care facilities have shown a relatively high prevalence of hyponatraemia, 16-34% of the older adults in the acute hospital setting and 18% of the nursing home residents can present this disorder.[1-4]

Physiological processes that occur with ageing are associated with changes in water metabolism and electrolyte balance, leading to alterations in plasma osmolality and body-fluid compartment volumes. Ageing typically leads to a 5-10% increase in total body fat, and a decrease in total body water of equal magnitude. In an elderly 70-kg man, this can account for a reduction in total body water of as much as 7-8 litres compared with a young man of the same weight.[5] The consequence of these changes is that an equivalent acute loss, or gain, of body water can cause a greater degree of flux in osmolality in elderly compared with younger individuals. In this way, states of relatively mild dehydration or volume overload in the older adults are more likely to cause clinically significant shifts in the concentration of body electrolytes, such as sodium. Ageing is characterised by impaired homeostasis to stress in different organ systems and physiological functions. The complex mechanisms associated with water metabolism can be particularly vulnerable to age-related impaired homeostasis and to the various disease processes and medical interventions that frequently occur in the elderly.

Several mechanisms can increase the risk of dehydration in older adults, such as the decreased thirst mechanism,[6] and the decrease in maximal urinary concentrating ability.[7] Also the ability to excrete a water load is delayed in the elderly.[8]

Eventually, structural and functional renal changes that increase susceptibility to alterations of water imbalance are decreased renal mass,[9] cortical blood flow[10] and glomerular filtration rate[11] as well as impaired responsiveness to sodium balance.[10] The impact of a lifetime of accumulated disease and comorbidities must also be considered in every clinical situation with elderly patients. The elderly patient has a diminished reserve of water balance and an impaired regulatory mechanism. Thirst sensation, concentrating abilities and hormonal modulators of salt and water balance tend to be less effective and susceptible to being overtaken by morbid or iatrogenic events.

In the present issue of *The Netherlands Journal of Medicine*, Brouns and colleagues report their findings on the prevalence, clinical presentation and treatment of hyponatraemia in elderly patients referred to the emergency department of a teaching hospital.[12]

The signs and symptoms of hyponatraemia can vary depending on the severity and duration of the condition; they include headache, nausea, vomiting, muscle cramps, disorientation, depressed reflexes, seizures and coma.[13] The symptoms, and any complications which may develop as a result, reflect the underlying cerebral pathophysiology of the hyponatraemia.[13,14]

Several authors have reported associations between mild hyponatraemia and gait instability (and consequent falls), attention deficits, and an increased risk of fractures due to osteoporosis in older adults.[15-17]

Brouns and colleagues found hyponatraemia to be common among elderly patients admitted to the internal medicine ward (26.3%) and associated with a long hospital stay. Moreover, they found that hyponatraemia was independently associated with higher mortality in older patients (increased mortality rate 54% when compared with the reference category). The results of this study show that the clinical implications of hyponatraemia in

hospitalised elderly patients are significant: hyponatraemia is an indicator of poor prognosis and therefore might be considered a marker of frailty in elderly patients. Despite being the most common electrolyte disorder in clinical practice, hyponatraemia is sometimes underdiagnosed and undertreated. Diagnostic evaluation of hyponatraemia in older patients with comorbidities and polypharmacy can be challenging and requires a systematic approach.

Clinicians need to use a systematic approach in evaluating water and sodium disorders, utilising a comprehensive assessment, and directed laboratory tests to make the clinical diagnosis. With the exponential increase of the elderly population and the consequent increasing incidence of hyponatraemia, prospective studies are needed to investigate whether the correction of hyponatraemia in the elderly will reduce the incidence of cognitive impairment, disability and mortality. Hyponatraemia can no longer be considered to be just a biochemical finding.

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REVIEW

Hepatocellular carcinoma: Dutch guideline for surveillance, diagnosis and therapy

F.A.L.M. Eskens[1]*, K.J. van Erpecum[5], K.P. de Jong[7], O.M. van Delden[8], H.J. Klumpen[9], C. Verhoef[2], P.L.M. Jansen[10], M.A.A.J. van den Bosch[6], A. Méndez Romero[3], J. Verheij[11], E. Bloemena[12], R.A. de Man[4]

Department of [1]Oncology, [2]Surgery, [3]Radiotherapy, and [4]Gastroenterology and Hepatology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands, Department of [5]Gastroenterology and Hepatology, and [6]Radiology, University Medical Centre, Utrecht, the Netherlands, [7]Department of Surgery, University Medical Centre, Groningen, the Netherlands, Department of [8]Radiology, [9]Oncology, [10]Gastroenterology and Hepatology, and [11]Pathology, Academic Medical Centre, Amsterdam, the Netherlands, [12]Department Pathology, VU University Medical Centre, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)10-7034897, fax: +31 (0)10-7034627, e-mail: f.eskens@erasmusmc.nl

ABSTRACT

Hepatocellular carcinoma (HCC) is rare in the Netherlands, even though the incidence has increased quite sharply in recent years. Standard treatment options consist of surgery, orthotopic liver transplantation, radiofrequency ablation, transarterial chemoembolisation (TACE) and systemic therapy with sorafenib. The consensus-based Dutch HCC guideline, established in 2013, serves to guide surveillance, diagnosis and treatment options:

- Surveillance should be performed by ultrasound at six-month intervals in well-defined cirrhotic patients and in selected high-risk hepatitis B carriers;
- A nodule > 1 cm in cirrhotic patients with arterial hypervascularity and venous or delayed phase washout at four-phase CT or MRI scan establishes the diagnosis of HCC;
- In patients with HCC without underlying cirrhosis, resection should be considered regardless of tumour size;
- In cirrhotic HCC patients, tumour stage, severity of underlying cirrhosis, and performance status determine treatment options. The algorithm of the Barcelona Clinic Liver Cancer (BCLC) staging system should be followed;
- Patients with Child-Pugh A-B cirrhosis (CP < 8 points) and performance status 0-2 are candidates for any active treatment other than transplantation;
- In early stage HCC (BCLC stage 0 or A, compensated cirrhosis without portal hypertension) surgical resection, liver transplantation, or radiofrequency ablation should be considered;
- In intermediate stage HCC (BCLC stage B) TACE and/or radiofrequency ablation should be considered;
- In advanced stage HCC (BCLC stage C) sorafenib should be considered.

Conclusion: The Dutch HCC guideline offers advice for surveillance, diagnosis and treatment of HCC.

KEYWORDS

Diagnosis, hepatocellular carcinoma (HCC), surveillance, treatment

INTRODUCTION

Primary liver cancer is the sixth most common cancer in the world and the third cause of cancer-related death.[1] Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers. Liver transplantation and resection are curative treatment options in HCC. In practice, only a minority of patients with HCC fulfil the criteria for potential cure.

Patients with HCC within the 'Milan criteria' (one nodule < 5 cm or up to three nodules each < 3 cm in diameter without macroscopic vascular invasion or extrahepatic disease) can be considered for liver transplantation. Resection of HCC is not possible in case of decompensated cirrhosis or portal hypertension.

Several local treatment options for unresectable HCC have been introduced in recent years. With radiofrequency ablation, a thin probe is inserted (generally percutaneously) under ultrasound or computed tomography (CT) guidance

in the tumour, and local ablation is obtained by heating to 60-100 °C.[2] With transarterial chemoembolisation (TACE), a catheter is placed in the feeding artery of the tumour. With radioembolisation or selective internal radiotherapy (SIRT), a catheter is placed in the artery supplying the tumour.[3,4] Treatment is pursued through local application of chemotherapy or radiotherapy, and in case of TACE combined with arterial embolisation. A cure is rarely obtained with TACE or SIRT, and currently SIRT is still considered to be an experimental treatment. In advanced or metastatic HCC, systemic therapy with the multi-tyrosine kinase inhibitor sorafenib leads to improvement in overall survival in selected patients.[5,6]

In 2011, a national committee with representatives of nurses and relevant medical specialists was installed in order to define a Dutch HCC guideline for surveillance, diagnosis and treatment of HCC. This committee was supported by the Comprehensive Cancer Centre of the Netherlands.

The Dutch HCC guideline has been approved by all relevant Dutch scientific associations and was published in 2013.[7,8] In this article we summarise the most important recommendations from this guideline.

EPIDEMIOLOGY

Incidence rates of HCC are highest in East Asia and Sub-Saharan Africa, where approximately 85% of all cases occur. Endemic risk factors such as chronic hepatitis B virus infection and aflatoxin B1 in the diet explain the high incidence.[1,9] In the Western world, hepatitis C, non-alcoholic steatohepatitis and alcohol are the predominant risk factors.[10] Coexisting metabolic syndrome can further increase HCC risk in patients with underlying liver disease.[11] Smoking is a factor leading to increased HCC risk, whereas the use of cholesterol synthesis inhibitors, oral antidiabetic agents and coffee consumption are associated with decreased HCC risk.[12-16]

Between 1989-2009, HCC was diagnosed in 5143 patients in the Netherlands. Potential curative treatment (liver resection, liver transplantation, radiofrequency ablation) was offered to 9% of patients in the period 1989-1994 and 23% in the period 2005-2009, whereas palliative treatment (sorafenib, TACE, radiotherapy) was offered to 6% of patients in the period 1989-1994 and 11% in the period 2005-2009. The percentage of patients to whom only supportive care could be offered decreased from 85% in the period 1989-1994 to 66% in the period 2005-2009. Between 1989-2009, one-year and five-year HCC survival rates increased from 20 to 37% and from 5 to 14%, respectively.[17]

SURVEILLANCE

Despite the introduction of new treatment modalities, survival in patients with advanced HCC remains poor. Thus preventive strategies are urgently needed to decrease the incidence of HCC. Primary prevention of HCC can be achieved by hepatitis B vaccination, and effective antiviral treatment of chronic viral hepatitis is associated with decreased HCC risk in these patients.[18-21] In patients at increased risk of developing HCC due to the presence of chronic liver disease, such as cirrhosis, surveillance by means of ultrasound can detect HCC at an earlier stage.[22] However, surveillance remains controversial because of limited evidence for its efficiency and the potential risk of side effects (due to unnecessary invasive procedures).[23,24] Even though the majority of HCC occurs in patients with underlying cirrhosis, about one out of three cases of HCC in the Netherlands occurs in patients without cirrhosis, hampering the efficacy of screening programs which are only pursued in patients with known underlying risk factors.[25] Ultrasound has been found to have a sensitivity of 63% to detect HCC within the 'Milan criteria'. Sensitivity is 70% in case of a six-month interval and 50% with a 6-12 month interval.[24]

According to the Dutch HCC guideline, surveillance should be offered to patients with cirrhosis due to chronic hepatitis B or C, haemochromatosis, alcohol or primary biliary cirrhosis, as well as to a high-risk hepatitis B virus carriers (*table 1*).[7] In patients with cirrhosis due to non-alcoholic steatohepatitis, autoimmune hepatitis, alpha1-antitrypsin deficiency and Wilson's disease, there is currently no

Table 1. *Recommendations for surveillance. Ultrasound with six-month intervals should only be performed in patients with strongly increased risk of HCC*[26]

Patients with chronic hepatitis B.
All patients with chronic hepatitis B and cirrhosis.
The following groups of patients with chronic hepatitis B without cirrhosis:
• Males from East Asia > 40 years old
• Females from East Asia > 50 years old
• Patients from sub-Sahara Africa > 20 years old
• Patients with a family history of HCC
Non-hepatitis B cirrhosis
• Hepatitis C
• Alcoholic cirrhosis
• Haemochromatosis
• Primary biliary cirrhosis

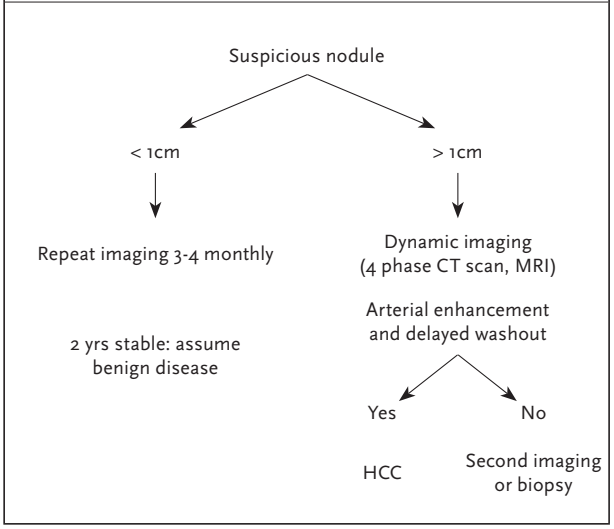
evidence to support surveillance. Moreover, in patients with cirrhosis due to non-alcoholic steatohepatitis, ultrasound is often unreliable due to excessive body weight. There are no data supporting surveillance with CT scan or magnetic resonance imaging (MRI). Surveillance through serial measurements of alpha-fetoprotein is not recommended.

DIAGNOSIS

If a nodule is detected by ultrasound in a high-risk patient with cirrhosis, radiological investigation by four-phase CT scan (with unenhanced, arterial, venous and delayed phases) and/or dynamic MRI scan is indicated to establish the diagnosis of HCC (*figure 1*). The combination of arterial hypervascularity with venous or delayed phase wash-out is pathognomonic for HCC. Varying results for the sensitivity and specificity of three-phase CT scan (sensitivity 50-87%, specificity 53-87%) and MRI scan (sensitivity 34-100%, specificity 62-100%) have been published.[7] Diagnostic accuracy has improved in the past decade as a result of an improvement in technology. In general, sensitivity and specificity will increase with increasing tumour size, whereas the positive and negative predictive value of a diagnostic procedure will strongly depend on the size of the lesion and the *a priori* HCC incidence in the investigated population. If diagnostic uncertainty remains, one may choose to monitor the lesion at 3-4 month intervals to detect growth.

Despite encouraging preliminary results, contrast-enhanced ultrasound is not recommended as a standard diagnostic due to limited experience and data.[7] PET/CT scan is also not recommended as a standard diagnostic imaging test.

Figure 1. *Diagnostic algorithm in case of a suspicious nodule in a patient with increased a priori risk of HCC*



If the diagnosis of HCC cannot be established by means of adequate radiodiagnostic procedures, a tumour biopsy may be considered. It is obvious that adequate tissue sampling and subsequent pathological assessment and reporting are mandatory under these circumstances, and thus it is recommended to perform these procedures only in specialised centres. According to a recent meta-analysis, needle tract seeding occurs in 2.7%, without any effect on patient survival.[27]

The diagnostic protocol is summarised in *figure 1*. In the Dutch HCC guideline, quality standards are given for CT scan, MRI scan, pathology assessment and reporting of results. Recommendations for diagnosis can be summarised as follows:

- Dynamic MRI scan or four-phase CT scan are advised for establishing the diagnosis of HCC;
- In patients with an increased *a priori* risk of HCC, a nodule > 1 cm in diameter with arterial hypervascularity and venous or delayed phase wash-out establishes the diagnosis. If results are inconclusive, one may choose radiological follow-up at 3-4 month intervals or (in expert centres) taking a biopsy of the nodule;
- In case of a nodule < 1 cm in diameter, radiological follow-up at 3-4 month intervals is recommended.

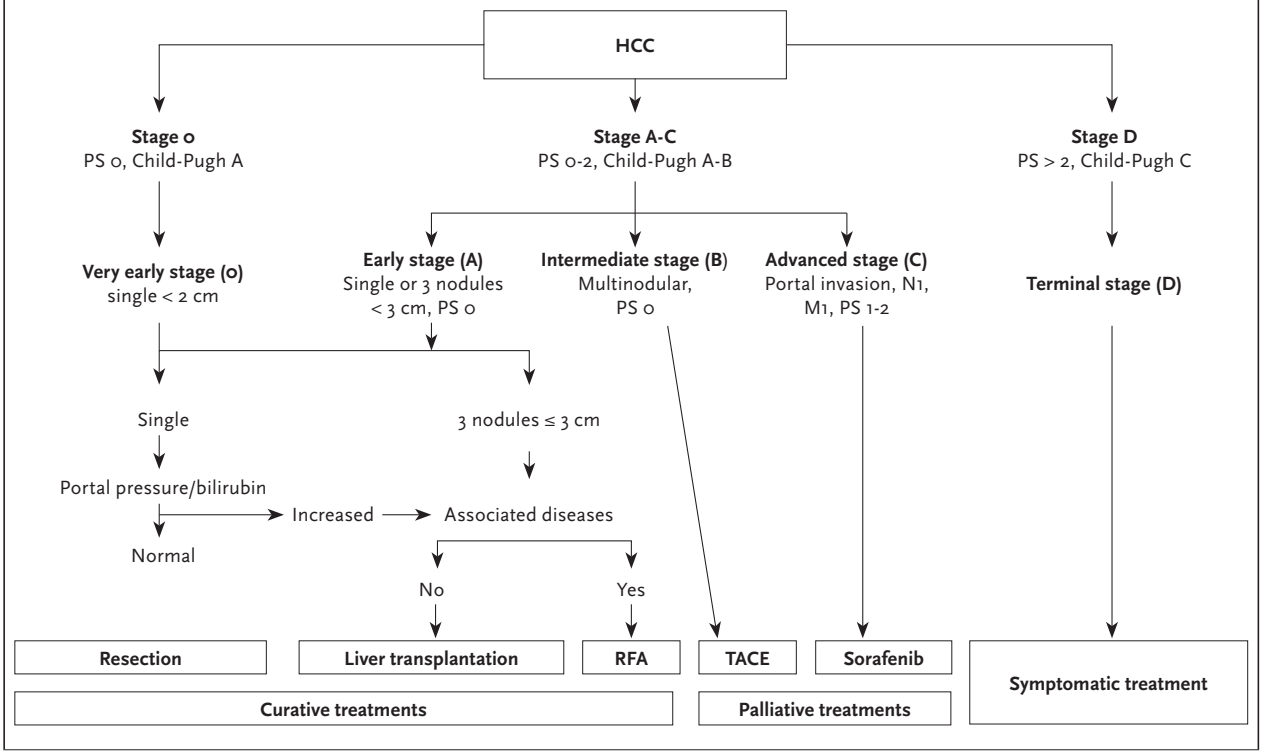
TREATMENT

In Western countries, the presence of a resectable solitary HCC nodule in a non-cirrhotic liver occurs in approximately 30% of all HCC cases. These patients can usually be treated with curative intent (generally resection), regardless of tumour size. In patients with a potentially resectable HCC lesion with underlying cirrhosis, however, not only tumour size, but also the severity of underlying liver disease and performance status must be taken into consideration. The Barcelona Clinic Liver Cancer (BCLC) staging system is the algorithm of choice to determine therapeutic options for patients with HCC and underlying cirrhosis (*figure 2*).[28] This validated staging system takes into account such relevant parameters as liver functionality (often as a consequence of underlying liver cirrhosis), tumour burden, clinical performance and divides patients into very early/early, intermediate, advanced, and end-stage. In general, only patients with Child-Pugh A-B cirrhosis (preferably CP < 8 points) and performance status 0-2 are candidates for any active treatment other than liver transplantation.

(Very) early stage (stage 0 or A, within 'Milan criteria')

Resection, transplantation and radiofrequency ablation can offer a cure to these patients.[29-33] Resection should only be performed in centres of expertise in patients with

Figure 2. *Treatment options for patients with early, intermediate, advanced or terminal stage HCC depend on BCLC (Barcelona Clinic for Liver Cancer) criteria, incorporating tumour stage, performance status and severity of underlying liver disease*



compensated (Child-Pugh A) cirrhosis in the absence of portal hypertension. For indication and selection for liver transplantation, we refer to: http://www.mdl.nl/uploads/240/846/Levertransplantatie_Protocol_indicatiestelling_en_selectie_maart_938 2011.pdf. The Dutch HCC guideline advises radiofrequency ablation in patients with, at most, moderately compromised liver function (CP class < 8) and with HCC within the 'Milan criteria' if liver transplantation or resection are not possible. It should be noted that radiofrequency ablation can also be performed as 'bridge to transplantation', considering the long waiting times for transplantation in the Netherlands. Also, based upon available literature, radiofrequency ablation is generally preferred over percutaneous ethanol injection, laser-induced thermotherapy or microwave coagulation.[7]

Intermediate stage (BCLC stage B: outside 'Milan criteria', but no macrovascular invasion or extrahepatic disease: median survival without therapy 15 months)

Several systematic reviews (including randomised controlled studies) indicate increased survival with TACE when compared with best supportive care.[3,34] However, a recent Cochrane review did not show survival benefit for TACE.[35] This Cochrane review included some studies with unusual patient characteristics and/or relatively short follow-up.

According to the Dutch HCC guideline, radiofrequency ablation can be considered in the intermediate stage with up to three tumour nodules and maximal diameter < 5 cm, provided the Child-Pugh score is less than 8. Considering the limited data available, the Dutch HCC guideline still advises TACE for intermediate stage HCC, especially in case of tumour diameter exceeding 5 cm, while acknowledging that this advice remains controversial. Also, in selected cases, initial TACE may enable subsequent radiofrequency ablation, resection or even liver transplantation by reducing tumour size. Although TACE with drug-eluting beads is more expensive than conventional TACE, and without survival benefit, the Dutch HCC guideline advises drug-eluting beads because of the lower risk of side effects such as liver toxicity and doxorubicin-related systemic side-effects.

Advanced stage HCC (BCLC stage C: invasion portal vein and/or extrahepatic disease, Child-Pugh A-B, performance status maximal 2: median survival without treatment 6 months)

Two randomised controlled studies have shown increased overall survival for sorafenib compared with best supportive care in patients with advanced HCC.[5,6,36] Based upon these data, the Dutch HCC guideline states that sorafenib should be considered for patients with

Table 2. *Child-Pugh classification for chronic liver disease*

Parameter	1 point	2 points	3 points
Serum total bilirubin (µmol/l)	< 34	34-50	> 50
Serum albumin (g/l)	> 35	28-35	< 28
INR	< 1.7	1.7-2.3	> 2.3
Ascites	none	Mild	Moderate to severe
Hepatic encephalopathy	none	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)

Table 3. *ECOG Performance Status*

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

compensated (Child-Pugh A) cirrhosis and advanced stage disease with performance status of 0-2. Patients with Child-Pugh B cirrhosis should preferably be treated in clinical trials based upon limited available data in this group. In addition, sorafenib can be considered for patients with compensated cirrhosis and intermediate stage disease, in case of progressive disease after loco-regional therapy (TACE, radiofrequency ablation) or if such locoregional therapy is not possible for technical or medical reasons.[37]

Terminal stage (BCLC stage D: Child-Pugh stage C, performance state > 2: median survival < 3 months)
For patients with terminal stage disease, the only option is best supportive care. These patients should not be treated with any active tumour-directed therapy.

INNOVATIVE TREATMENT OPTIONS

Promising results have been reported in uncontrolled studies for such treatment options as stereotactic radiotherapy, selective internal radiotherapy or radioembolisation with Yttrium-90, microwave coagulation therapy and laser-induced thermotherapy. The Dutch HCC guideline advises that these innovative treatments should only be applied in clinical trials.

CONCLUSION

The Dutch HCC guideline offers advice for surveillance, diagnosis and treatment of HCC. In addition, the Dutch Working Party on Hepatocellular Carcinoma has initiated and facilitated multidisciplinary communication, concept and design for a national registry, and meanwhile various preclinical and clinical study initiatives are pursued under its umbrella.

DISCLOSURES

All authors declared no conflict of interest, commercial affiliations, consultations, stock or equity interests.

Additional members of the Dutch working party hepatocellular carcinoma:
W. Bakker, former director of the Dutch Liver Patients Association
G. Koerts, T.M.J. Kleijwegt, Erasmus Medical Centre, Rotterdam
M.A. van der Pol, G.H. Schrier, S. Janssen-van Dijk, Comprehensive Cancer Centre of the Netherlands

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ORIGINAL ARTICLE

Accuracy of aPTT monitoring in critically ill patients treated with unfractionated heparin

S. van Roessel[1]*, S. Middeldorp[1], Y.W. Cheung[1], A.H. Zwinderman[2], A.C.J.M. de Pont[3]

Department of [1]Vascular Medicine, [2]Clinical Epidemiology, Biostatistics and Bioinformatics, and [3]Intensive Care, Academic Medical Center, Amsterdam, the Netherlands, *corresponding author: tel: +31 (0)6-13042692, e-mail: s.vanroessel@amc.uva.nl

ABSTRACT

Introduction: The anticoagulant effect of unfractionated heparin (UFH) is usually monitored by means of the activated partial thromboplastin time (aPTT). In critically ill patients, however, increased levels of acute phase proteins may decrease the accuracy of the aPTT, leading to inadequate UFH dosing. In these circumstances, the anti-Xa assay is recommended for monitoring.

Objective: We aimed to analyse the accuracy of the aPTT for the monitoring of UFH dosing in critically ill patients.

Methods: In critically ill patients treated with therapeutic doses of UFH, we compared aPTT levels with simultaneously measured anti-Xa levels as the gold standard. Sensitivity and specificity of the aPTT were determined for different cut-off points, receiver operating characteristic (ROC) curves were constructed and their areas under the curve (AUCs) were calculated.

Results: A total of 171 paired blood samples from 58 patients were analysed. Concordant aPTT and anti-Xa values were observed in 108 (63.2%) data pairs. In 33 data pairs (19.3%) the aPTT was discordantly high and in 30 data pairs (17.5%) discordantly low. The sensitivity of the aPTT in detecting UFH underdosing and overdosing was 0.63 and 0.37, respectively. When considering alternative thresholds, ROC curves for underdosing and overdosing had AUCs of 0.71 and 0.81, respectively.

Conclusion: In this small cohort of critically ill patients, the aPTT was accurate in 63.2% of the blood samples. Its sensitivity to detect UFH underdosing and overdosing was low (0.63 and 0.37, respectively). We conclude that in critically ill patients, the aPTT is not accurate enough to detect UFH underdosing and overdosing.

KEYWORDS

Heparin/therapeutic use, partial thromboplastin time, factor Xa/analysis, drug monitoring/methods, critical care

INTRODUCTION

Although unfractionated heparin (UFH) has been replaced by low-molecular-weight heparin (LMWH) for many indications, it remains the anticoagulant of choice among selected patient groups because of its short half-life and its possibility to be reversed by protamine sulphate.[1] The indications for UFH may ultimately be limited to clinical environments in which rapid reversal of the anticoagulant effect is required, e.g. the intensive care unit (ICU). Despite being a cornerstone of anticoagulation, UFH is limited by its unpredictable pharmacokinetic profile. The complex kinetics of clearance render the anticoagulant response to heparin nonlinear at therapeutic doses, with both the intensity and duration of the effect rising disproportionately with increasing dose.[2] The anticoagulant and pharmacological properties of UFH vary among patients as well as within individuals over time, as a consequence of the binding of UFH to various plasma proteins.[3]

Because of its unpredictable anticoagulant effect, close monitoring of UFH treatment is crucial. Historically, the activated partial thromboplastin time (aPTT) has been the primary laboratory test used to monitor and adjust UFH.[4] A therapeutic aPTT range of 1.5-2.5 times baseline has gained wide acceptance in daily clinical practice.[2,5]

Monitoring of the anti-factor Xa effect has been suggested as an alternative to the aPTT because the assay is based on enzymatic inhibition, which can be accurately measured spectrophotometrically using well-defined chemical reagents that are not biologically derived.[6] Since the anti-factor Xa assay measures the inhibition of a single enzyme, it reflects the UFH activity more directly than the aPTT. Accordingly, it demonstrates less variability and exhibits minimal interference from the presence of biological factors, such as acute phase reactants.[7] Disadvantages of the anti-factor Xa assay are its relative expense and limited laboratory availability.

Because of their complex clinical presentation, critically ill patients are particularly vulnerable and difficult to manage. These patients have a predisposition for thrombosis due to acquired risk factors including indwelling central venous catheters, prolonged immobilisation and acquired coagulation disorders.[8] They are also susceptible to bleeding complications because of acquired coagulopathy, drug interactions, recent surgery or invasive procedures and concomitant organ failure, especially of the liver or kidney. Renal failure affects the anticoagulant effect of UFH due to decreased clearance. Moreover, critically ill patients often have decreased levels of albumin, increasing the serum concentration of unbound drugs and thus the risk of toxicity. On the other hand, critically ill patients often have elevated levels of acute phase proteins such as factor VIII. Binding of UFH to these acute phase proteins may contribute to heparin resistance, resulting in an even more unpredictable response of UFH in critically ill patients. Aforementioned complications contribute to the morbidity and mortality in critical care patients and close monitoring is required to protect these patients against adverse outcomes.

The accuracy of the aPTT for monitoring of UFH dosing in critically ill patients is currently not well-known and we hypothesised that it is insufficient. Therefore, we assessed the accuracy of the aPTT in terms of sensitivity and specificity for detecting underdosing and overdosing of UFH in critically ill patients.

MATERIALS AND METHODS

Study design

We conducted a retrospective observational study using the data of critically ill patients admitted to the Academic Medical Center (AMC), a 1000-bed university hospital in Amsterdam, the Netherlands. All patients who received intravenous UFH in the intensive care unit and medium care unit of the AMC between January 2010 and January 2012 were eligible for this study. We identified patients by a query in the hospital laboratory database, searching for patients in whom both an aPTT and an anti-Xa level were measured. We excluded patients aged under 18 years and patients treated with anticoagulants other than UFH.

Laboratory assays

In all patients, we compared the results of aPTT and anti-Xa levels performed on the same blood sample in our routine haemostasis laboratory. All blood samples were drawn into sodium citrate tubes (BD Vacutainer, Becton Dickinson Co.) then centrifuged at 2680 g at 20 °C for 15 minutes to separate blood cells from platelet-poor plasma; the aPTT was then analysed. To obtain platelet-free plasma the plasma was transferred into another tube and further centrifuged for 5 minutes at 13,000 g at 20 °C followed by storage at -30 °C until anti-Xa assays were performed. Coagulation parameters were measured using a Sysmex CA-7000 system (Siemens AG, Erlangen, Germany) with Dade Actin FS activated PTT reagent (Siemens AG, Erlangen, Germany) for the aPTT and STA liquid anti-Xa reagent (Diagnostica Stago SAS, Asnières sur Seine, France) for the anti-Xa. aPTT levels between 45-60 seconds and anti-Xa levels between 0.3-0.7 IU/ml were defined as therapeutic.

Protocols

According to the ICU heparin dosing protocol, the treating physician sets and documents the target aPTT level for each patient in the patient data management system. Depending on indication and risk of bleeding, a loading dose of 1000-5000 units is administered, followed by a continuous infusion of 1000 units/hour. The aPTT is measured four times a day starting four hours after the start of infusion, even when the aPTT result is within the therapeutic range. The dose-adjustment protocol is shown in *table 1*.

Data collection and outcomes

The primary outcome assessed in this study was the accuracy of the aPTT in monitoring UFH dosing, using the anti-Xa level (0.3-0.7 IU/ml) as gold standard. Paired aPTT and anti-Xa measurements were grouped according to their concordance. Discordantly paired measurements were divided into two subgroups:

- Disproportionately low aPTT values (i.e. a subtherapeutic aPTT with a therapeutic or high anti-Xa level or a therapeutic aPTT with a supratherapeutic anti-Xa level);

Table 1. *Protocol for the intravenous dosing of unfractionated heparin – ICU Academic Medical Center Amsterdam*

aPTT result	Dose modification*	Follow-up after
< 39	Increase drip by 150 IU/h, consider bolus 1000-5000 IU	6 h
39-44	Increase drip by 100 IU/h	6 h
45-59	–	6 h
60-74	Decrease drip by 50 IU/h	6 h
75-89	Decrease drip by 100 IU/h, stop infusion for ½ hour	6 h
> 89	Decrease drip by 150 IU/h, stop infusion for 1 hour	6 h

***Initial dosing: infusion rate of 1000 IU/h or 5 ml/h with a concentration of 200 IU/ml. Bolus: administration of a bolus depends on the indication and is not given without consultation of the treating physician.**

- Disproportionately high aPTT values (i.e. a therapeutic aPTT with a subtherapeutic anti-Xa level or a supratherapeutic aPTT with a subtherapeutic or therapeutic anti-Xa level).

Since a disproportionately low aPTT value is unable to detect UFH overdosing, this result represents a risk of bleeding. The opposite is true for a disproportionately high aPTT value, which represents a risk of thrombosis. Patients were divided into groups according to their concordance status and clinical outcomes were assessed.
For further assessment of the diagnostic value of the aPTT, we determined the sensitivity and specificity of the aPTT for detecting underdosing and overdosing of UFH, using the anti-Xa as a gold standard.

Statistical analysis
Statistical analysis was conducted with SPSS version 20.0 (IBM Inc., Chicago, Illinois, USA). Because there were multiple measurements per patient and the number of aPTT and anti-Xa measurements differed between patients, we used a generalised linear mixed model to estimate specificity and sensitivity. Data are presented as median and range. Instead of the commonly used thresholds to define normal aPTT levels, we also determined sensitivity and specificity for both detecting underdosing and overdosing by means of the aPTT for multiple cut-off values. Based on these data, receiver operating characteristic (ROC) curves were constructed and for each of them the area under the curve (AUC) was calculated. A p-value < 0.05 was considered statistically significant.

RESULTS

Fifty-eight patients met the inclusion criteria and were enrolled in the study (*table 2*). Concomitant use of LMWH was the most prevalent reason for exclusion. The main indications for UFH therapy were venous thromboembolism (41.4%) and atrial fibrillation (32.8%).
Paired measurements of aPTT and anti-Xa were performed on 171 samples and plotted as an x-y scatterplot. The distribution of aPTT and anti-Xa levels is shown in *figure 1*. The median aPTT was 48 seconds (range: 22-96), the median anti-Xa level was 0.3 IU/ml (range: 0.1-1.0) and the median administered UFH dose was 1600 IU/hour (range: 900-2600 IU/hour). For each anti-Xa value, a wide range of aPTT values was measured. For an anti-Xa level of 0.4 IU/ml, for example, the corresponding aPTT values ranged from 32-65 seconds.
In *table 3*, the concordance of the test results is shown. Concordant aPTT and anti-Xa values were observed in 108 (63.2%) data pairs, whereas in 33 data pairs (19.3%) the aPTT was discordantly high and in 30 data pairs (17.5%) discordantly low.
When UFH was monitored by the aPTT, underdosing was detected in 32 out of 56 samples (57%), whereas the anticoagulant efficacy was underestimated in 22 of 115 samples (19%). Using the generalised mixed model, we calculated the sensitivity and specificity of the aPTT to detect UFH underdosing to be 0.63 and 0.82, respectively.

Table 2. *Baseline characteristics*

Patients, n	**58**
Age in years, median (range)	61 (25-86)
Male, n (%)	37 (64)
Weight in kg, median (range)	85 (50-134)
Indication for anticoagulation	
VTE, n (%)	24 (41.4)
Atrial fibrillation, n (%)	19 (32.8)
Mechanical heart valve, n (%)	10 (17.2)
Acute coronary syndrome, n (%)	2 (3.4)
Unknown, n (%)	3 (5.2)
Admission diagnosis	
Infection or inflammation, n (%)	27 (46.6)
Heart valve replacement, n (%)	8 (13.8)
Acute coronary syndrome, n (%)	6 (10.3)
Arterial thrombosis, n (%)	6 (10.3)
Other cardiovascular, n (%)	5 (8.6)
Malignant neoplasm, n(%)	2 (3.4)
Other, n (%)	4 (6.9)
Severity score (APACHE II)	
< 12, n (%)	6 (10.3)
12-17, n (%)	22 (37.9)
18-22, n (%)	10 (17.2)
> 22, n (%)	14 (24.1)
Unknown, n (%)	6 (10.3)

APACHE II = Acute Physiology and Chronic Health Evaluation II; VTE = venous thromboembolism.

Figure 1. *Distribution of aPTT and anti-Xa levels in an XY scatter plot*

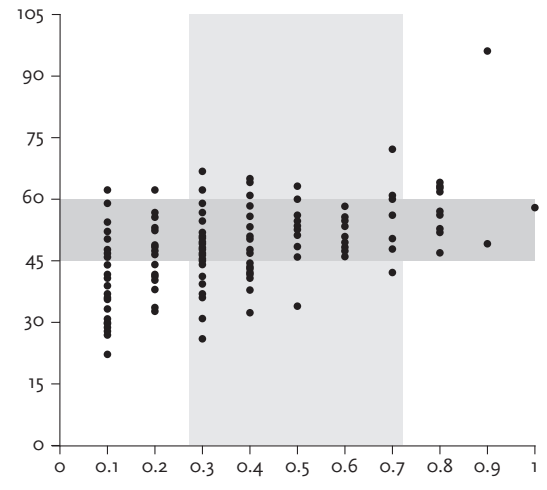

Table 3. *Cross-tabulation of clinically relevant aPTT and anti-Xa levels*

aPTT, s	Total	anti-Xa <0.3 IU/ml	anti-Xa 0.3-0.7 IU/ml	anti-Xa > 0.7 IU/ml
< 45	54	32	22	0
45-60	102	22	72	8
> 60	15	2	9	4
Total	171	56	103	12
Detecting heparin underdoing and overdosing with the aPTT			Sensitivity (GLMM)	Specificity (GLMM)
UFH underdosing (anti-Xa < 0.3 IU/ml)			0.63	0.82
UFH overdosing (anti-Xa > 0.7 IU/ml)			0.37	0.94

GLMM = general linear mixed model; UFH = unfractionated heparin.

UFH overdosing was detected by means of the aPTT in four out of 12 samples (33%), whereas in 11 out of 159 samples, overdosing was falsely diagnosed (7%). After statistical correction for repeated measurements, we found a sensitivity of 0.37 and specificity of 0.94 for detecting UFH overdosing by means of the aPTT. ROC curves for detecting UFH underdosing and overdosing had AUCs of 0.71 and 0.81, respectively (*figure 2*). The highest combination of sensitivity and specificity was reached with an aPTT cut-off value of 45 seconds for detecting UFH underdosing (sensitivity 0.81, specificity 0.57) and 51 seconds for detecting UFH overdosing (sensitivity 0.83, specificity 0.69).

To further evaluate the accuracy of the aPTT, the occurrence of thrombosis and bleeding was assessed. In *table 4*, the number of thrombotic and bleeding events is related to the concordance status of the patients. Forty-three patients (74.1%) had mainly concordant aPTT and anti-Xa values, nine patients (15.5%) had mainly disproportionately low aPTT values and six patients (10.3%) had mainly disproportionately high aPTT values. There was no statistically significant difference in the occurrence of thrombotic and bleeding events between these three groups.

We also calculated the sensitivity and specificity of the aPTT and anti-Xa for detecting thrombotic and bleeding events. The results of these calculations are shown in *table 4*. The majority of bleeding events were haematomas without further adverse outcomes. One patient suffered from gastrointestinal bleeding causing a decrease in haemoglobin concentration, for which an intervention was required.

DISCUSSION

The aim of laboratory monitoring of anticoagulation is to ensure an optimal antithrombotic effect while minimising the risk of bleeding.[1] In the present retrospective study, we examined the accuracy of the aPTT in critically ill patients requiring high doses of UFH, using the anti-Xa level as gold standard. In patients on UFH, we noted discordance between aPTT and anti-Xa assays in 36.8% of the paired measurements. Discordantly high and low aPTT values were found in 19.3 and 17.5% of the blood samples, respectively. The aPTT had a sensitivity of 0.63 and a

Figure 2. *ROC curve for A) Detecting UFH underdosing (anti-Xa < 0.3 IU/ml) by means of the aPTT, B) Detecting UFH overdosing (anti-Xa > 0.7 IU/ml) by means of the aPTT*

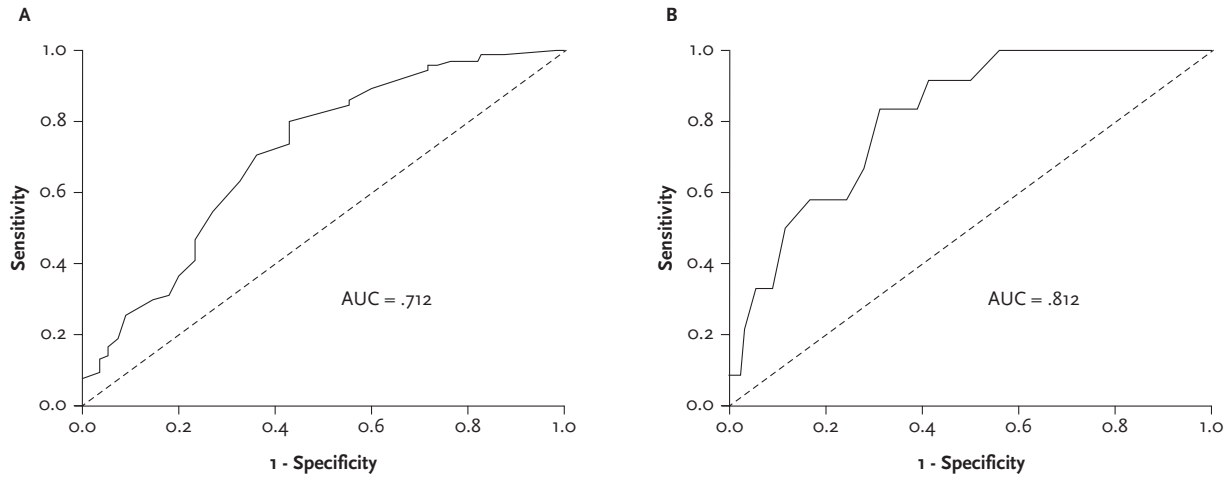

Table 4. *Clinical outcome of the patients according to their concordance status*

Group of patients	Number of patients	Thrombotic events	Bleeding events
Discordantly high aPTT levels			
aPTT > 60 and anti-Xa < 0.7 or	2	-	2
aPTT > 45 and anti-Xa < 0.3	7	1	-
Concordant aPTT levels			
Subtherapeutic (anti-Xa < 0.3)	11	2	-
Therapeutic (anti-Xa 0.3-0.7)	31	2	5
Supratherapeutic (anti-Xa > 0.7)	1	-	1
Discordantly low aPTT levels			
aPTT < 45 and anti-Xa > 0.3 or	4	-	-
aPTT < 60 and anti-Xa > 0.7	2	-	1
Total	58	5	9
		Sensitivity	Specificity
Detecting a thrombotic event			
By means of the aPTT		0.40 (2 out of 5)	0.81 (43 out of 53)
By means of the anti-Xa		0.60 (3 out of 5)	0.68 (36 out of 53)
Detecting a bleeding event			
By means of the aPTT		0.33 (3 out of 9)	0.96 (47 out of 49)
By means of the anti-Xa		0.22 (2 out of 9)	0.96 (47 out of 49)

specificity of 0.82 for detecting UFH underdosing. In order to detect UFH overdosing, we found a low sensitivity (0.37) but a high specificity (0.94). Considering other aPTT thresholds to define overdosing or underdosing, the ROC curves for underdosing and overdosing had AUCs of 0.71 and 0.81, respectively. The highest combination of sensitivity and specificity for detecting underdosing and overdosing was reached with an aPTT cut-off value of 45 and 51 seconds, respectively.

The results of our study are in line with results of previous studies on this subject.[9,10] Takemoto *et al.* found a poor correlation between aPTT and anti-Xa and elucidated which acute phase reactants were associated with a disproportionately low and high aPTT. The study demonstrated that low factor II activity resulted in a discordantly high aPTT for a given anti-Xa activity level. Conversely, discordantly low aPTT values were noted for a given anti-Xa in the presence of elevated factor VIII activity.[10] Since our study had a retrospective nature, we were unable to investigate the interaction with acute phase reactants in our patients. According to other studies, critically ill patients often have aberrant levels of acute phase proteins, which may lead to a shortened or a prolonged aPTT.[11-13] Although there is a relationship between the UFH level and the aPTT, the relationship is weak and the aPTT is associated with both significant intra- and inter-patient variability.[7,14]

Although the aPTT is considered a global assessment of coagulation status, it is not designed to detect either a thrombotic or a bleeding event. The anti-Xa level represents the level of heparinisation and does not reflect either thrombosis or bleeding. Therefore, the cross-tabulation with clinical outcomes should be considered an overview of the clinical outcomes according to the patient's coagulation status rather than an evaluation of the diagnostic value to detect thrombosis or a bleeding. Conflicting data exist about higher heparin doses or excessively prolonged aPTT and its effect on haemorrhagic risk.[15-17] However, patient-specific factors are likely to be important contributors to the bleeding risk in patients on UFH treatment, with increased risk of bleeding seen in the context of older age,[18] concomitant treatment with antiplatelet drugs[19] and the presence of other haemostatic defects.[20]

Since our study involved multiple measurements per patient, we had to conduct a specific statistical analysis to reduce the potential bias of repeated measurements. There was no significant bias from multiple measurements per patient, suggesting that multiple measurements were included from individuals with both concordance and discordance. However, the analysis of variance did slightly increase the sensitivities of detecting both UFH underdosing and overdosing with the aPTT when compared with the raw statistics. This is the result of a situation with a smaller intra-patient variability than the inter-patient variability. A repeated measurements design increases the sensitivity of a test when subjects serve as their own controls, and thus inter-subject variation is not a problem.[21]

The limitations of our study merit some consideration. First, this analysis was designed as a pilot study to investigate the accuracy of the aPTT in patients admitted to the ICU. Because of the small sample size, the probability of a type II error is conceivable. Consequently, it should be recognised that showing a reduction in thrombosis or bleeding according to the patient's coagulation status based on the aPTT or anti-Xa would require an extremely large, prospective study design. Second, anti-Xa assays were only performed in patients in whom a discordantly low aPTT was suspected. This may have caused a significant bias in the selection of patients. To obtain an unbiased judgment of the value of the aPTT, paired measurements of aPTT and anti-Xa should be compared in all patients treated with UFH.

Another limitation is that the outcomes analysed in this study are based on surrogate markers of heparin effect, rather than in terms of clinical outcomes such as rates of thrombosis and bleeding. Since there is a lack of evidence about clinical outcomes related to anti-Xa levels, open questions remain about whether the anti-Xa should be considered to be the gold standard. In a population of patients aged less than 1 year, Gruenwald *et al.* found no correlation between whole blood heparin concentrations and anti-Xa levels.[22]

Although UFH overdosing does not occur often, the aPTT is not adequate to detect UFH overdosing, with a low sensitivity of 0.37. Conversely, UFH underdosing occurs more often, but the aPTT is also unreliable to detect this effect, with a sensitivity of 0.63. Although an AUC of 0.81 seems somehow reliable for detecting overdosing by means of the aPTT, it should be considered that the ROC curve is a combination of sensitivity and specificity. Therefore, a high specificity for several cut-off values can result in a reasonable AUC, despite the fact the sensitivity is dramatic for most cut-off values.

In conclusion, in critically ill patients, the aPTT is less accurate than the anti-Xa in detecting UFH underdosing and overdosing. We suggest to use the anti-Xa assay for the monitoring of UFH treatment in critically ill patients with an increased risk of bleeding.

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DISCLOSURE

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ORIGINAL ARTICLE

Hyponatraemia in elderly emergency department patients: A marker of frailty

S.H.A. Brouns[1]*, M.K.J. Dortmans[1], F.S. Jonkers[1], S.L.E. Lambooij[1], A. Kuijper[1], H.R. Haak[1,2,3]

[1]Department of Internal Medicine, Máxima Medical Centre, Eindhoven/Veldhoven, the Netherlands, [2]Department of Internal Medicine, Division of General Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands, [3]Maastricht University, Department of Health Services Research, and CAPHRI School for Public Health and Primary Care, Maastricht, the Netherlands, *corresponding author: tel.: +31 (0)408-886300, fax: +31 (0)40-2450385, e-mail: S. Brouns@mmc.nl

ABSTRACT

Background: Details on hyponatraemia in the emergency department are limited, especially regarding older patients, a population more susceptible to hyponatraemia and its effects. Our objective was to gain insight into the prevalence, aetiology, treatment and prognosis of clinically relevant hyponatraemia in elderly emergency department patients. The impact of the severity of hyponatraemia on outcome was a secondary objective.

Methods: A retrospective cohort study of 1438 internal medicine patients aged ≥ 65 years presenting to the emergency department between 1 September 2010 and 31 August 2011 was performed. Clinically relevant hyponatraemia was defined as a serum sodium level < 130 mmol/l. The reference group had a serum sodium level of 130-145 mmol/l. Hyponatraemia was subdivided into moderate (129-125 mmol/l), and severe (< 125 mmol/l).

Results: Ninety-one elderly patients (6.3%) were hyponatraemic at presentation to the emergency department. The main causes were the use of diuretics, hypovolaemia, and the syndrome of inappropriate antidiuretic hormone secretion (57.1%). Hyponatraemia was associated with higher admission rates (93.4 vs. 72.9%) and longer hospital stay (8 vs. 6 days) vs. the reference group. Three-month survival rate in hyponatraemic elderly patients was 74% (95% CI 64-84%) vs. 83% (95% CI 81-85%) in the reference group. Moderate hyponatraemia was associated with an increased risk of death (HR 1.7, 95% CI 1.2-2.4) vs. the reference group after multivariable adjustment for age and comorbidity.

Conclusion: Hyponatraemia, a common electrolyte disturbance among elderly internal medicine patients presenting to the emergency department, was associated with higher admission rates, longer hospital stay, and higher mortality rates. In particular, moderate hyponatraemia was a marker of underlying frailty and predictive of mortality.

KEYWORDS

Emergency department, frail elderly, hyponatraemia, outcome

INTRODUCTION

Hyponatraemia is the most common electrolyte disturbance encountered in clinical practice.[1] The prevalence of hyponatraemia varies widely depending on the clinical setting. The highest frequencies are observed in intensive care unit (ICU) patients, in the postoperative setting, and in older patients admitted to geriatric wards.[2,3] The elderly are particularly susceptible to developing hyponatraemia, due to age-related physiological changes in water and electrolyte balance, the presence of comorbid conditions, and polypharmacy.[4-6]

Diagnostic evaluation of hyponatraemia can be challenging, especially in elderly patients with multi-morbidity, and requires a systematic approach, including assessment of the extracellular volume status and distinction between acute and chronic hyponatraemia.[7-9] Although mild stable hyponatraemia is often considered to be of little clinical significance, recent studies have identified an association between hyponatraemia and complications, such as falls due to gait instability, attention deficits, and an increased risk of fractures due to osteoporosis.[1,10,11] These complications may be of special significance to frail older patients with hyponatraemia. Furthermore, severe hyponatraemia is a marker of serious disease and an indicator of poor prognosis.[12-15] Nonetheless, it remains unclear whether the higher mortality rates encountered in severe hyponatraemia are directly related to deviations in sodium levels or to underlying conditions.[14,16]

Information on the frequency of hyponatraemia and its impact on outcome in elderly patients in an emergency department setting is limited. Yet, this information is essential in implementing a strategy to prevent adverse health outcome in this vulnerable population. The primary goal of our study was to gain insight into the prevalence, aetiology, clinical presentation, and treatment of clinically relevant hyponatraemia in elderly medical patients presenting to the emergency department. Differences in the presentation and outcome of elderly patients with hyponatraemia versus elderly patients with normal serum sodium levels and the impact of the severity of hyponatraemia on patient outcome were secondary objectives.

MATERIALS AND METHODS

Study design, setting and selection of participants

A retrospective cohort study was conducted at a 500-bed teaching hospital in the Netherlands. The majority of emergency department patients are referred by a general practitioner. Other modes of presentation are referral by a medical specialist, ambulance arrival in high emergency patients, and self-referral. Patients presenting to the emergency department are assessed by an intern, a non-trainee resident, or a trainee resident supervised by a medical specialist or emergency physician.

Data on all visits of patients aged 65 years or older referred to the emergency department for internal medicine between 1 September 2010 and 31 August 2011 were extracted by two abstractors with a medical background. The abstractors were not blinded to the study hypothesis. Patients were excluded if internal medicine was not the principle treating speciality in the emergency department. The presence of hyponatraemia was identified by laboratory investigation in the emergency department. After identification of elderly patients with hyponatraemia in the emergency department, only data on the index visit were extracted. Follow-up lasted from the date of the emergency department visit until the end of at least one year of follow-up, the date of death, or the date of last available information. Institutional Review Board exemption of approval was acquired.

Covariates

Information on baseline characteristics, medical history, and medication use as assessed in the emergency department, the date and time of the visit, clinical characteristics at presentation to the emergency department, laboratory investigation performed in the emergency department, diagnosis and hospital discharge diagnosis, serum sodium levels during admission, discharge date, and the date of last follow-up or the date of death were retrieved from patient records. The index visit was defined as the first emergency department visit of each patient between 1 September 2010 and 31 August 2011. Triage at presentation was performed using the five-level Manchester Triage System (MTS).[17,18] Medical history and comorbidity as recorded in patients' emergency department records were classified according to the International Classification of Disease-10 (ICD-10) and according to the Charlson Comorbidity Index (CCI), which consists of the following categories: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accidents, pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, severe liver disease, diabetes mellitus (with and without complications), hemiplegia or paraplegia, cancer, metastatic cancer, and human immunodeficiency virus (HIV).[19] Polypharmacy was defined as the use of five or more different medications.[20]

Outcomes

The focus of the study was clinically relevant hyponatraemia, defined as a serum sodium level < 130 mmol/l. Moderate and severe hyponatraemia were defined as serum sodium levels between 125-129, and < 125 mmol/l, respectively. Elderly patients with a serum sodium level between 130-145 mmol/l were assigned to the reference group. Normonatraemia was defined as a serum sodium level between 135-145 mmol/l. Hypernatraemia was defined as a serum sodium level > 145 mmol/l.[8]

The objective of the study was to estimate the prevalence, aetiology, treatment, and correction rate of clinically relevant hyponatraemia, hospital admission, the length of hospital stay, in-hospital mortality rate, and three-month and one-year survival. In a secondary analysis, we compared hyponatraemic patients with the reference group. Data on vital status to at least one-year follow-up were obtained from patient records or by contacting their general practitioners. If the date of death was unknown, the date in between the date of the last follow-up and the date of contact with the general practitioner was selected.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0. Armonk, New York. Comparisons of baseline patient characteristics between hyponatraemic patients and the reference group and between the hyponatraemic severity groups were made using the Chi-square for categorical variables. Numerical variables were tested using one-way analysis of variance, the Kruskal-Wallis test, Mann-Whitney U test, and unpaired T-test, depending on the number of groups compared and the distribution pattern of the variable. Missing data were categorised as 'unknown' and included in the analyses. The prevalence of hyponatraemia was

calculated by dividing the number of hyponatraemic elderly patients by the total number of elderly patients included in the study; 95% confidence intervals (95% CI) of the prevalence were estimated assuming a normal distribution.[21] Overall survival was estimated using the Kaplan-Meier survival analysis. The log-rank test was used to compare survival curves. Univariable and multivariable Cox regression analyses were performed in order to estimate the effect of covariates on patient outcome, expressed as hazard ratio (HR) and 95% CI. Multivariable analysis included all variables associated with the outcome in the univariable analysis at a p-value of 0.1 and changing the point estimate by > 10% in bivariable analysis, or variables considered as clinically relevant. Effect modulation was investigated. A p-value < 0.05 was considered significant. A sensitivity analysis was performed to evaluate the effect of missing sodium values on patient survival by including patients with missing values in the reference group in the analysis.

RESULTS

Characteristics of study subjects

During the study period, 1438 index visits of patients aged 65 years and older presenting to the emergency department for internal medicine were identified. The reference group consisted of 1218 elderly patients. Ninety-one elderly patients were hyponatraemic (mean age 78.4 years), representing a prevalence of 6.3% (95% CI 5.2-7.7%). Serum sodium level was unknown in 84 elderly patients and 45 elderly patients were hypernatraemic. In 91 hyponatraemic patients, 58 (63.7%) were classified as moderate, and 33 (36.3%) as severe hyponatraemia.

In seven patients (7.7%), the main reason for the emergency department visit was hyponatraemia. Malaise was the most prevalent symptom, namely in 15 patients (16.5%). Other reasons for the visit in hyponatraemic elderly patients included confusion or delirium in seven patients (7.7%), hyperglycaemia in three patients (3.3%),

Table 1. *Baseline characteristics of elderly patients presenting at the emergency department*

	Total (n = 1309)	Hyponatraemia (n = 91)	Reference group (n = 1218)	P-value
Mean age in years (SD) Range	77.8 (7.7) 65-99	78.4 (7.5) 65-94	77.7 (7.8) 65-99	0.447
Male patients (%)	589 (45.0%)	24 (26.4%)	565 (46.4%)	< 0.001
Medical history (%)				
No history	11 (0.8%)	1 (1.1%)	10 (0.8%)	0.860
Unknown	3 (0.3%)	-	3 (0.3%)	
Diabetes mellitus	308 (23.5%)	31 (34.1%)	277 (22.7%)	0.040
Dementia	76 (5.8%)	2 (2.2%)	74 (6.1%)	0.235
Heart failure	121 (9.2%)	11 (12.1%)	110 (9.0%)	0.488
Malignancy	358 (27.3%)	29 (31.9%)	329 (27.0%)	0.480
Respiratory condition	192 (14.7%)	10 (11.0%)	182 (14.9%)	0.443
Mean CCI (SD)	2.2 (2.1)	2.5 (2.3)	2.2 (2.1)	0.335
Medication use (%)				
Polypharmacy	766 (58.5%)	59 (64.8%)	707 (58.0%)	0.448
Unknown	119 (9.1%)	7 (7.7%)	112 (9.2%)	
Diuretics	489 (37.4%)	50 (55.6%)	439 (36.1%)	0.001
Antipsychotics	42 (3.2%)	3 (3.3%)	39 (3.2%)	0.719
Antidepressants	102 (7.8%)	6 (6.6%)	96 (7.9%)	0.616
Mean number (SD)	6.3 (3.8)	6.7 (3.8)	6.3 (3.8)	0.270
Referral (%)				
General practitioner	955 (73.0%)	73 (80.2%)	882 (72.4%)	0.189
Medical specialist	87 (6.6%)	7 (7.7%)	80 (6.6%)	
Ambulance	131 (10.0%)	7 (7.7%)	124 (10.9%)	
Self-referral	136 (10.4%)	4 (4.4%)	132 (10.8%)	
Triage by MTS (%)				
Red	16 (1.2%)	1 (1.1%)	15 (1.2%)	0.700
Orange	133 (10.2%)	11 (12.1%)	122 (10.0%)	
Yellow	744 (56.8%)	56 (61.5%)	688 (56.5%)	
Green	413 (31.6%)	23 (25.3%)	390 (32.0%)	
Blue	-	-	-	
No triage	3 (0.2%)	-	3 (0.3%)	

SD = standard deviation; CCI = Charlson Comorbidity Index; MTS = Manchester Triage System: red = immediate resuscitation, orange = very urgent, yellow = urgent, green = standard, blue = non-urgent.
P-value for comparison of elderly patients with hyponatraemia and the reference group. P-values were estimated using the unpaired T-test, Mann-Whitney U test, and Chi-square test.

collapse or fall in four patients (4.4%), and somnolence in two patients (2.2%). Most patients presented with symptoms unrelated to hyponatraemia.

Twenty-four hyponatraemic patients (26.4%) were male compared with 565 (46.4%) in the reference group ($p < 0.001$) (*table 1*). The comorbidity index was comparable among hyponatraemic elderly patients and the reference group (mean CCI 2.5 vs. 2.2, respectively, $p = 0.335$). Diuretic use was more frequent in hyponatraemic patients than in the reference group (55.6 vs. 36.1%, respectively, $p < 0.001$). Hyponatraemic elderly patients were more often diabetic compared with the reference group (*table 1*). Hyponatraemic elderly patients had a higher C-reactive protein level (44.5 vs. 23 mg/l, respectively, $p = 0.022$) than the reference group. Primary diagnoses made in the emergency department were similar in hyponatraemic elderly patients and the reference group. Fifty-three elderly patients (3.7%) were lost to follow-up, of which 47 (3.9%) patients were in the reference group, one (1.1%) was hyponatraemic, two (4.4%) were hypernatraemic, and for three (3.6%) patients, sodium level was unknown.

Elderly patients with unknown serum sodium levels (n = 84) were younger (75.9 vs. 77.7 years, respectively, $p = 0.035$) than elderly patients in the reference group. They had lower comorbidity levels (mean CCI 1.5 vs. 2.2, respectively, $p = 0.005$) and were less frequently admitted to the hospital (29.8 vs. 72.9%, respectively, $p < 0.001$). The most common presenting symptom was (suspected) deep venous thrombosis (n = 23, 27.4%), as opposed to malaise in patients for whom sodium data were available.

Aetiology and treatment

A minority of patients received an advanced diagnostic work-up in the emergency department to determine the cause of hyponatraemia, such as measurement of blood osmolality (22.0%), urine osmolality (23.1%), and urine sodium (45.1%). The presumed cause of the hyponatraemia was specified in the emergency department charts of 62 patients (68.1%). The use of diuretics was considered the primary cause (n = 25, 27.5%), followed by hypovolaemia (n = 14, 15.4%) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) (n = 13, 14.3%). Other causes were hyperglycaemia (n = 2, 2.2%), renal insufficiency (n = 2, 2.2%), and heart failure (n = 3, 3.3%).

In 83.5% of the hyponatraemic elderly patients (n = 76), therapy to correct the serum sodium was started in the emergency department. The most frequently used method of correction (n = 28, 30.8%) was a combination of the infusion of isotonic sodium chloride (0.9% NaCl) and cessation of medication; 26.4% of elderly patients (n = 24) received 0.9% NaCl infusion. Other methods of correction were cessation of medication (n = 6, 6.6%), fluid restriction (n = 7, 7.7%), hypertonic sodium chloride infusion (3% NaCl) (n = 4, 4.4%), or other combination therapy (n = 7, 7.7%). Treatment time in the emergency department was similar for hyponatraemic patients and the reference group (median 161 vs. 162 minutes, respectively, $p = 0.450$) and hyponatraemic patients with and without a cause specified (162 vs. 159 minutes, respectively, $p = 0.655$).

The median initial rate of sodium correction in the severe hyponatraemia group (n = 32) was 0.53 mmol/l/hour (range 0.06-2.8 mmol/l/hour) during the first ten hours of correction. In nine patients with severe hyponatraemia (27.3%), the rate of correction exceeded 10 mmol/l/24 hours. No patients developed osmotic demyelination syndrome. Six (6.6%) elderly patients were discharged home from the emergency department with hyponatraemia. Eleven hyponatraemic patients (15.3%) still had a serum sodium level < 130 mmol/l at time of hospital discharge.

Patient outcome

Hyponatraemia in elderly emergency department patients was associated with higher admission levels (93.4 vs. 72.9%, respectively, $p < 0.001$) and longer median hospital

Table 2. *Outcome in hyponatraemic elderly patients vs. the reference group*

	Total (n = 1309)	Hyponatraemia (n = 91)	Reference group (n = 1218)	P-value
Hospital admission (%)	973 (74.3%)	85 (93.4%)	888 (72.9%)	< 0.001
Median length of hospital stay in days (range)	6 (1–91)	8 (1–64)	6 (1–91)	0.021
ICU/MCU admission (%)	32 (3.3%)	2 (2.4%)	30 (3.4%)	0.051
Death during admission (%)	96 (9.9%)	13 (15.3%)	83 (9.3%)	0.087
ED return visits < 3 months (%)	316 (24.1%)	14 (15.4%)	302 (24.8%)	0.085
Three-month survival (95% CI)	82% (80–84%)	74% (64–84%)	83% (81–85%)	
One-year survival (95% CI)	68% (66–70%)	53% (43–63%)	69% (67–71%)	

ICU = Intensive Care Unit, MCU = Medium Care Unit, SD = standard deviation, 95%CI = 95% confidence interval. P-values for comparison of outcome in elderly patients with hyponatraemia and the reference group. P-values were estimated using the Mann-Whitney U test and Chi-square test. One-year survival was calculated with Kaplan-Meier analysis.

stay (8 vs. 6 days, respectively, p = 0.021) compared with the reference group (*table 2*). Hospitalised elderly patients with hyponatraemia (n = 85) had higher triage levels compared with hyponatraemic patients who were discharged home from the emergency department (n = 6). Comorbidity levels and medication use were comparable among hospitalised and discharged hyponatraemic elderly patients. The three-month survival rate of hyponatraemic elderly patients directly discharged from the emergency department was 100 vs. 72% (95% CI 62-82%) in hospitalised hyponatraemic elderly patients. The in-hospital mortality rate of elderly patients with hyponatraemia was 15.3% (n = 13), in contrast to 9.3% (n = 83) in older patients from the reference group (p = 0.087). Three-month and one-year survival in all hyponatraemic elderly patients were 74% (95% CI 64-84%) and 53% (95% CI 43-63%) vs. 83% (95% CI 81-85%) and 69% (95% CI 67-71%) respectively in the reference group. Complete (n = 61) or incomplete (n = 11) correction of the sodium level during hospitalisation did not influence one-year survival (57%, 95% CI 45-69% vs. 73%, 95% CI 48-98%, respectively). After multivariable adjustment for age and CCI, and a combination of age, CCI and C-reactive protein, hyponatraemia was independently associated with higher mortality rates among elderly patients (HR 1.5, 95% CI 1.1-2.1 and HR 1.5, 95% CI 1.1-2.0) compared with the reference group (*table 3*). Sensitivity analysis, performed to evaluate the effect of missing sodium values on patient outcome, revealed no change in one-year survival (70%, 95% CI 68-72%), when considering all patients with unknown sodium values as part of the reference group.

Table 3. *Unadjusted and adjusted hazard ratio and 95% confidence intervals for mortality in hyponatraemic elderly patients compared with the reference group.*

	Total (n = 91)	Moderate (n = 58)	Severe (n = 33)
Crude HR	1.5 (1.1–2.0)	1.7 (1.2–2.4)	1.2 (0.7–2.1)
Age-adjusted	1.5 (1.1–2.0)	1.6 (1.1-2.2)	1.2 (0.7–2.1)
CCI-adjusted	1.6 (1.2–2.2)	1.8 (1.2–2.5)	1.3 (0.8–2.2)
Malignancy-adjusted	1.5 (1.1–2.1)	1.6 (1.1–2.3)	1.4 (0.8–2.4)
CRP-adjusted	1.4 (1.0-1.9)	1.5 (1.1-2.2)	1.1 (0.7-2.0)
Multivariable adjusted 1	1.5 (1.1-2.1)	1.7 (1.2-2.4)	1.3 (0.8-2.3)
Multivariable adjusted 2	1.5 (1.1–2.0)	1.5 (1.1-2.2)	1.3 (0.7-2.2)

1 Adjusted for age and CCI, 2 Adjusted for age, CCI, and CRP levels. HR = hazard ratio, 95%CI = 95% confidence interval, CCI = Charlson Comorbidity Index, CRP = C-reactive protein.
Variables initially considered as potential confounders: referral pattern, gender, history of diabetes, respiratory condition and heart failure, total number of medications, polypharmacy, and diuretics.

Subgroup analysis of hyponatraemia categories

CCI and diuretic use were comparable among patients with moderate and severe hyponatraemia (*table 4*). Severely hyponatraemic patients presented more often to the emergency department with symptoms related to hyponatraemia (36.4%) compared with moderately hyponatraemic patients (22.4%). Diagnostic work-up was increasingly complete with worsening of serum sodium (*table 4*). The C-reactive protein level was 78.5 mg/l in moderate, and 12 mg/l in severe hyponatraemia. In 29 (87.9%) of the severely hyponatraemic patients, the aetiology of the sodium disorder was registered in

Table 4. *Characteristics of elderly patients, subdivided into moderate, and severe hyponatraemia*

	Moderate (n = 58)	Severe (n = 33)	P-value
Mean age in years (SD)	78.8 (7.8)	77.6 (7.0)	0.191
Male patients	15 (25.9%)	9 (27.3%)	1.000
Medical history (%)			
Heart failure	8 (13.8%)	3 (9.1%)	0.740
Dementia	1 (1.7%)	1 (3.0%)	1.000
Diabetes mellitus	18 (31.0%)	13 (39.4%)	0.492
Malignancy	22 (37.9%)	7 (21.2%)	0.109
Respiratory condition	4 (6.9%)	6 (18.2%)	0.160
Mean CCI (SD)	2.5 (2.1)	2.3 (2.5)	0.640
Medication use (%)			
Polypharmacy	37 (63.8%)	22 (66.7%)	0.837
Unknown	4 (6.9%)	3 (9.1%)	
Diuretics	32 (56.1%)	18 (54.5%)	0.964
Total number (SD)	6.6 (4.0)	7.0 (3.6)	0.671
Diagnostic work-up on ED (%)			
Blood osmolality	8 (13.8%)	12 (36.4%)	0.018
Urine osmolality	10 (17.2%)	11 (33.3%)	0.119
Urine sodium	19 (32.8%)	22 (66.7%)	0.002
Cause of hyponatraemia (%)			0.002
No cause specified	25 (43.1%)	4 (12.1%)	
Diuretics	13 (22.4%)	12 (36.4%)	
Hypovolaemia	10 (17.2%)	4 (12.1%)	
SIADH	3 (5.2%)	10 (30.3%)	
Hyperglycaemia	1 (1.7%)	1 (3.0%)	
Renal insufficiency	2 (3.4%)	-	
Heart failure	2 (3.4%)	1 (3.0%)	
Other	2 (3.4%)	1 (3.0%)	
Admission (%)	53 (91.4%)	32 (97.0%)	0.411
Median hospital LOS in days (range)	9 (1-64)	7 (1-29)	0.492
Death during admission (%)	10 (18.9%)	3 (9.4%)	0.290
Three-month survival (95%CI)	74% (62-86%)	73% (57-89%)	

SD = standard deviation, ED = emergency department, CCI = Charlson Comorbidity Index, SIADH = syndrome of inappropriate antidiuretic hormone secretion, LOS = length of stay, CI = confidence interval. P-value for trend in comparison of moderate, and severe hyponatraemia. P-values were estimated using the unpaired T-test, Mann-Whitney U test, and Chi-square test

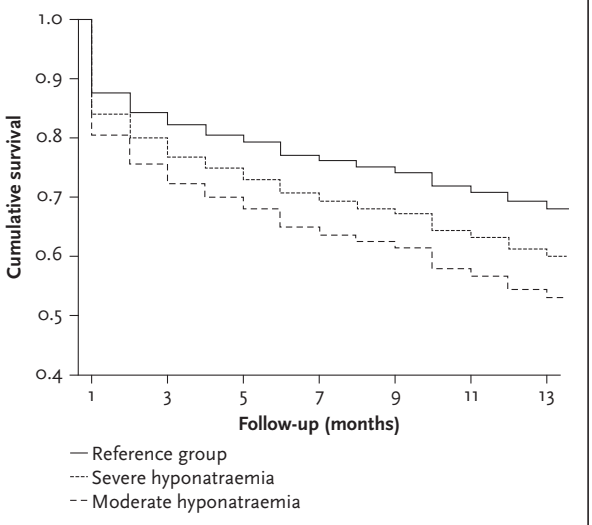
the emergency department, compared with 33 (56.9%) in moderate hyponatraemia (p < 0.002). The primary cause of severe hyponatraemia was the use of diuretics (n = 12, 36.4%), followed by SIADH (n = 10, 30.3%) and hypovolaemia (n = 4, 12.1%). Treatment was started in the emergency department in 32 (97.0%) of the patients with severe hyponatraemia, and 44 (75.9%) of the patients with moderate hyponatraemia (p = 0.015). Admission rates were similar in both hyponatraemia categories (*table 4*).

One-year survival was 50% (95% CI 36-64%), and 58% (95% CI 40-76%) for moderate, and severe hyponatraemia, respectively. Adjustment for age, CCI and a combination of age, CCI, and C-reactive protein levels revealed an increased risk of death in patients with moderate hyponatraemia (HR 1.7, 95% CI 1.2-2.4 and HR 1.5, 95% CI 1.1-2.2, respectively) vs. elderly patients in the reference population (*figure 1*) (*table 3*).

DISCUSSION

In this retrospective cohort study, we report a prevalence of clinically relevant hyponatraemia (serum sodium level < 130 mmol/l) of 6.3% in elderly internal medicine patients presenting to the emergency department. Research in hospitalised patients, focusing solely on elderly patients, reported a prevalence of 16.7-34.5%,[13,16,22,23] which is considerably higher than our results. However, comparison of our results remains difficult, since the cut-off value for hyponatraemia as well as the clinical setting vary among studies resulting in different prevalence rates.[7,24-27]

Figure 1. *Survival in patients with moderate, and severe hyponatraemia and the reference group after adjustment for age and CCI*



CCI = Charlson Comorbidity Index

Few elderly patients presented to the emergency department solely for analysis of hyponatraemia. This corresponds with findings that hyponatraemia was not an isolated disease, but rather an additional factor to an underlying disorder.[13] Remarkably, only a minority of patients received an appropriate diagnostic work-up according to the emergency department guideline.[28] In addition, the cause of hyponatraemia was specified in only 68.1% of hyponatraemic patients in the emergency department. Although both observations apply particularly to cases with moderate hyponatraemia, incomplete or lack of analysis could possibly lead to inadequate treatment in this group and consequently adverse patient outcome. However, due to the retrospective nature of the study, some of the clinical assessment steps in the emergency department were perhaps not accurately documented, but were in fact part of diagnostic work-up and treatment. In addition, we found an adequate median correction rate of 0.53 mmol/l/hour during the first ten hours of correction in severely hyponatraemic patients, the subgroup with the highest risk of complications.[28] Furthermore, even though the advised correction rate of 10 mmol/l/24 hours was exceeded in nine patients with severe hyponatraemia, no cases of osmotic demyelination syndrome occurred. Blood osmolality, however, was known in only 22.0% of hyponatraemic elderly, and therefore it was not possible to accurately identify pseudohyponatraemia or hyperosmolar hyponatraemia. Still, our analysis of all sodium values showed that hyponatraemia regardless of underlying pathophysiology is an adverse prognosticator in elderly emergency department patients.

Our study confirms previous findings that hyponatraemia is an indicator of poor prognosis, such as longer hospital stay and higher mortality rates.[14,24,26] In particular, patients with moderate hyponatraemia had the highest mortality rate compared with the reference group, even after adjustment for age, CCI, and C-reactive protein levels. We found no relationship between mortality in moderate hyponatraemia and the presence of an acute critical illness at emergency department presentation as is reflected by comparable triage levels among hyponatraemia groups. The increased mortality risk in elderly patients with moderate hyponatraemia may be due to a lack of guideline adherence, leading to underdiagnosing and undertreating of elderly patients with moderate hyponatraemia.[29] In addition, moderate hyponatraemia was frequently an additional finding in other underlying disorders. The therapy indicated for these disorders may not be appropriate for hyponatraemia. Moreover, the failure of physicians to identify the increased health risk associated with asymptomatic hyponatraemia in this frail population may contribute to adverse patient outcome. Since hyponatraemia, especially moderate hyponatraemia, is probably a good marker of frailty and a poor prognosis in older patients as is consistent with previous

research,[23] it emphasises the need to adequately assess and treat hyponatraemia in elderly patients, in addition to careful monitoring of their general condition.

Our findings may have been influenced by several limitations. Firstly, due to the single-centre setting, our findings may not be generalisable to other populations. Secondly, there is a potential for bias, because of the retrospective observational design and as a result of incomplete data. Furthermore, the inability to determine the specific reason for measuring sodium levels in this retrospective cohort is a potential source of bias. Additionally, because of the availability of nursing home physicians in the Netherlands, elderly nursing home residents may have been underrepresented, since these patients are less likely to be sent to the emergency department for evaluation. Therefore, the results of our study may not be applicable to this patient group. Moreover, despite our efforts to correct for confounders detected in previous research or encountered in this study, residual bias may remain. Lastly, the relatively small number of patients with severe hyponatraemia may contribute to reduced reliability of our results.

Future prospective research should focus on the impact of hyponatraemia on patient outcome specifically relevant to the elderly, such as the risk of cognitive and functional decline. In addition, whether improvement in the care of elderly hyponatraemic patients on the emergency department can result in a reduction of adverse outcome remains an important research question.

In summary, hyponatraemia is common among elderly internal medicine patients visiting the emergency department and is associated with adverse outcome. Moderate hyponatraemia seems to be of special importance to the elderly, as it appears to be a marker for frailty and predictive of mortality in this population. Improvement in adequately diagnosing and treating hyponatraemia in elderly emergency department patients is important, yet more attention to the general condition of this frail population is essential.

Disclosure

The authors declare no conflict of interest. No funding or financial support was received.

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ORIGINAL ARTICLE

The implementation of a comprehensive discharge bundle to improve the discharge process: a quasi-experimental study

K.J. Verhaegh[1], B.M. Buurman[1]*, G.C. Veenboer[2], S.E. de Rooij[1], S.E. Geerlings[3]

[1]Section of Geriatric Medicine, [2]Division of Renal Diseases and [3]Division of Infectious Diseases, Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-5665991, e-mail: b.m.vanes@amc.nl

ABSTRACT

Background: Hospitalised patients are especially vulnerable in times of transitions in care. Structured discharge planning might improve patient outcomes. We implemented and assessed the effect of a multidisciplinary discharge bundle to reduce 30-day readmission.

Methods: A pre-post-test design study with a follow-up of one month at four internal medicine wards in a Dutch university teaching hospital. Eligible patients were 18 years and older, acutely admitted and hospitalised for at least 48 hours. The discharge bundle consisted of (1) planning the date of discharge within 48 hours after admission, (2) a discharge checklist, (3) a personalised patient discharge letter, and (4) multidisciplinary patient education. The primary outcome measure was unplanned 30-day readmission.

Results: Participants in the post-test group (n = 204) did not have a lower rate of unplanned hospital readmission than those receiving usual care (n = 224) (12.9 vs. 13.2%, p = 0.93). The medical discharge summaries were sent to the general practitioner faster in the post-test period (median of 14 days pre-test vs. 5 days post-test, p < 0.001) and this group also had a trend towards a longer time to first readmission (14 vs. 10 days, p = 0.06). Patient satisfaction was high in both groups (7.5 and 7.4 points, (p = 0.49)).

Conclusions: The comprehensive discharge bundle was not effective in reducing the rate of readmission and increasing patient satisfaction, but medical discharge summaries were sent faster to the general practitioner and a trend to a longer time to readmission was present.

KEYWORDS

Hospital readmission, patient satisfaction, discharge planning, patient education, healthcare utilisation

INTRODUCTION

Over 20% of the patients who have been recently discharged from the hospital are readmitted within 30 days.[1,2] One in five patients experience an adverse event after discharge. Almost half of the adverse events are potentially preventable[3] and are likely to be associated with discontinuities in the discharge period, such as the lack of a standardised discharge planning,[4] pending test results at discharge,[5] medication changes during hospitalisations,[6] poor communication between hospital professionals and primary care providers[7,8] and between inpatient and outpatient pharmacies.[9] Furthermore, patients and their caregivers are often not prepared to perform self-care at discharge because they might have an inadequate understanding of their diagnosis, medications, and follow-up needs.[10] Currently, in the USA unplanned hospital readmission within a 30-day period is used as an outcome indicator for hospitals to assess quality of care and for some diagnoses, readmissions are not reimbursed under the Affordable Care Act.[11]

Research on improvement of the hospital discharge process[12-16] showed that structured discharge planning,[12] patient education,[13,14] medication reconciliation,[15] and programmed care follow-ups[16] are associated with a decrease of adverse events including readmission. Most of these studies were focused on specific patient populations or diagnoses or consisted of single-component interventions offered by one discipline.[12,15,16] Multidisciplinary interventions, joined in a so-called bundle of interventions addressing patient-centredness, effective communication and a standardised discharge process, seem to be more promising in reducing post-discharge emergency department visits and unplanned hospital readmissions together with increased patient satisfaction.[13,14,17,18]

The primary aim of this study in medical patients was to evaluate whether the implementation of a comprehensive discharge bundle was associated with a reduction of hospital readmission within 30 days of discharge. The secondary aim of our study was to evaluate the effect of the discharge bundle on duration of the readmission, time to readmission, length of stay, total number of general practitioner (GP) and emergency department visits, mortality, time until sending the medical discharge letter to the GP and patient satisfaction on the overall discharge process.

METHODS

Design and setting

This pre-post-test design study was conducted between September 2010 and December 2012 at four general medicine wards in the Academic Medical Center (AMC) in Amsterdam, the Netherlands, as in a previous comparable project.[19] The AMC is a 1024-bed university teaching hospital. The attending staff consisted of residents, registered nurses, and medical specialists. The study was subdivided into three time periods. The pre-test period ranged from September 2010 to March 2011, the intervention was implemented between April 2011 and January 2012, and the post-test period ranged from January 2012 to December 2012. After the post-test phase the discharge bundle was implemented on all wards throughout the whole hospital.

Patients

Eligible patients had to meet the following criteria: (1) 18 years or older, (2) acutely admitted at one of the four general medicine wards for more than 48 hours, (3) discharged home, (4) able to speak or understand Dutch, (5) have a working telephone, (6) showed no notification of cognitive impairment in the medical record, and (7) had an estimated life expectancy of more than three months. Written informed consent was obtained prior to enrolment. The study was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam, the Netherlands.

Data collection procedure

Data collection, performed by a trained research nurse, was equal in the pre-intervention and post-intervention period. The research nurse identified eligible patients daily before hospital discharge for the index admission and approached them in the hospital or by telephone within 48 hours of discharge to obtain informed consent. At discharge, a questionnaire was sent to their home address consisting of questions addressing (1) demographic variables, (2) patient satisfaction on the overall discharge procedure, (3) communication of the date of discharge, (4) the personalised patient discharge letter and (5) topics that were included in the verbal patient education before discharge. Four weeks after discharge patients were contacted once again for a follow-up telephone survey to assess the patient's hospital readmission and healthcare utilisation over a four-week period after hospital discharge. Baseline data of participants, including length of index hospital stay, admission diagnoses and comorbidities, were obtained at the time of recruitment by review of the hospital medical electronic file and discharge summaries. We determined the number of hospital admissions and emergency department visits in the six months before index admission through medical record review (AMC hospital utilisation) and calculated the Charlson Comorbidity Index (CCI) score by using primary and secondary diagnoses recorded on the index admission discharge summary.[20]

The pre-test group received standard level of personal health information and communication during hospital stay and discharge. This included a protocolised telephone follow-up within 48 hours after discharge to address critical questions or health problems of the patient and sending a medical discharge letter to the GP.

Construction of the discharge bundle

The discharge bundle was constructed based on focus group meetings with professionals, patient satisfaction surveys, and literature.[12-14,17,21,22] The bundle consisted of four elements: (1) planning the date of discharge within 48 hours after admission, (2) a discharge checklist for residents and nurses, (3) a personalised patient discharge letter and (4) patient education.

Concerning the first element, in collaboration with a nurse, the medical resident had to plan and communicate the date of discharge within 48 hours after admission to the patient and his/her caregiver, which was reviewed on a daily basis. The second element was a discharge checklist for residents and nurses in order to provide a uniform and standardised discharge procedure, which was developed in collaboration with residents and medical specialists and nurses of all four medical wards. A clear distinction was made between tasks and responsibilities for either physicians or nurses. The checklist contained all the proceedings organised in time schedules from admission to hospital discharge, which had to be completed in the electronic patient medical record before hospital discharge and took the planned date of discharge as the starting point.

Patient education was improved in two ways. Patients and their caregivers received a personalised patient discharge letter at discharge, the third element of the discharge bundle, which was a plain language handover and consisted of personalised information about diagnosis, tests, results, diet, medication, daily activities, warning

signs, date of clinical follow-up, home-based care, and contact information. Residents and interns were trained monthly in the use of this discharge letter. As part of the intervention, the personalised patient discharge letter was built into the electronic patient medical record and could also be sent digitally to the GP at discharge.

The fourth element, verbal patient education about diagnosis and treatment during hospital stay, lifestyle advice, (changes in) medication and early warning signs after discharge took place by the resident and nurse as a team. Topics of education were derived from the personalised patient discharge letter and discharge checklist, as a combination of written and verbal information has been shown to be most effective in educating patients how to manage their care at home.[23] Medication reconciliation was performed when providing the personalised patient discharge letter and during patient education.

Implementation strategies

Several activities were planned to ensure thorough implementation.[24] Firstly, the medical and nursing staff were educated about all four elements of the discharge bundle by the project coordinator (KV). Secondly, focus group meetings were held on a monthly basis with the leadership team to evaluate the implementation process. The leadership team consisted of the project coordinator, the staff nurses and medical specialist, one senior level registered nurse and three residents. Furthermore, personal visits to residents and their supervisors took place every two months to explain the bundle. The final purpose was to create a combination of tailored change strategies to sustain involvement in the implementation of the interventions and provide optimal support for the other nurses and residents. Thirdly, the personalised patient discharge letter was developed in collaboration with the leadership team, and it was included in the education of all medical Masters students. The checklist and personalised patient discharge letter were made electronically available.

Outcomes and definitions of outcomes

The primary endpoint was an unplanned hospital readmission within 30 days after discharge from the index hospitalisation. This was measured in two ways: (1) with data from the medical records and (2) with self-reports by the patients. Any emergency department visit in which a participant was subsequently hospitalised was counted as an unplanned readmission.

Secondary outcomes included length of initial hospital stay, time to readmission, number and duration of readmissions, total number of GP and emergency department visits, mortality, overall patient satisfaction of discharge process, and time until sending the medical discharge letter to the GP. Furthermore, patients reported on the topics that were covered during verbal patient education with closed and open questions using a standardised questionnaire. We assessed if participants who could not be reached by telephone were alive 30 days after hospital discharge through medical record review.

We conducted a structured process evaluation during the implementation of the discharge bundle with predefined process indicators[25,26] focused on the discharge process (e.g. number of patients in which the discharge checklist was completed and the personalised patient discharge letter and verbal patient education was provided). The results of these rates were discussed during the focus group meetings.

Data analysis

Descriptive statistics were obtained on the patient characteristics, differences between the pre- and post-test group were examined using Chi-square or Student t-tests. A two-sided p-value of < 0.05 was considered to be statistically significant. As we observed significant difference between the pre-test (control) and post-test (intervention) group at baseline, we adjusted the outcome analyses on unplanned 30-day readmission for important covariates. We performed a logistic regression analysis in which unplanned readmission (data from the medical records) served as dependent variable and the group allocation (pre-test or post-test) was the independent variable. Based on the literature,[27,28] the following variables as well as those which significantly differed between the two groups were treated as covariates: age, sex, ethnicity, living arrangements, discharge diagnosis, CCI score, total number of readmissions in the six months before the index admission, and length of stay. Because it is known from other studies that patients with a previous admission in the six months before the index admission are at increased risk for a readmission, we also performed a subgroup analysis on outcomes only including those high-risk patients. All analyses were conducted using SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

RESULTS

Patient characteristics

During the study period, 2678 patients from the four medical wards were assessed for eligibility. As listed in *figure 1*, 61% did not meet the study criteria because they were not admitted more than 48 hours (28%), were not discharged home (15%), could not speak or understand Dutch (3%), had a notification of cognitive impairment in the medical record (5%), or did not have an estimated life expectancy of more than three months (10%). Ultimately, 428 patients (224 in the pre-test period and 204 in the post-test period) were included in our study of which

30-day readmission data were complete for all 428 (100%) participants. *Table 1* compares the demographic and clinical characteristics of the study population. The pre- and post-test study groups showed significant differences in country of birth (p = 0.01), education level (p = 0.02), living arrangements (p = 0.04), and discharge diagnosis (p ≤ 0.001). No differences were present between the two groups on the number of hospital admissions in the preceding six months.

We had missing data on some outcomes; only 342 (80%) patients (161 pre-test and 181 post-test) provided data on GP and emergency department visits after 30 days and 237 (55%) patients (121 pre-test and 116 post-test) rated their satisfaction with the discharge procedure. No differences were present regarding age, sex, and comorbidity between the group with complete data, those

Figure 1. *Study flow diagram*

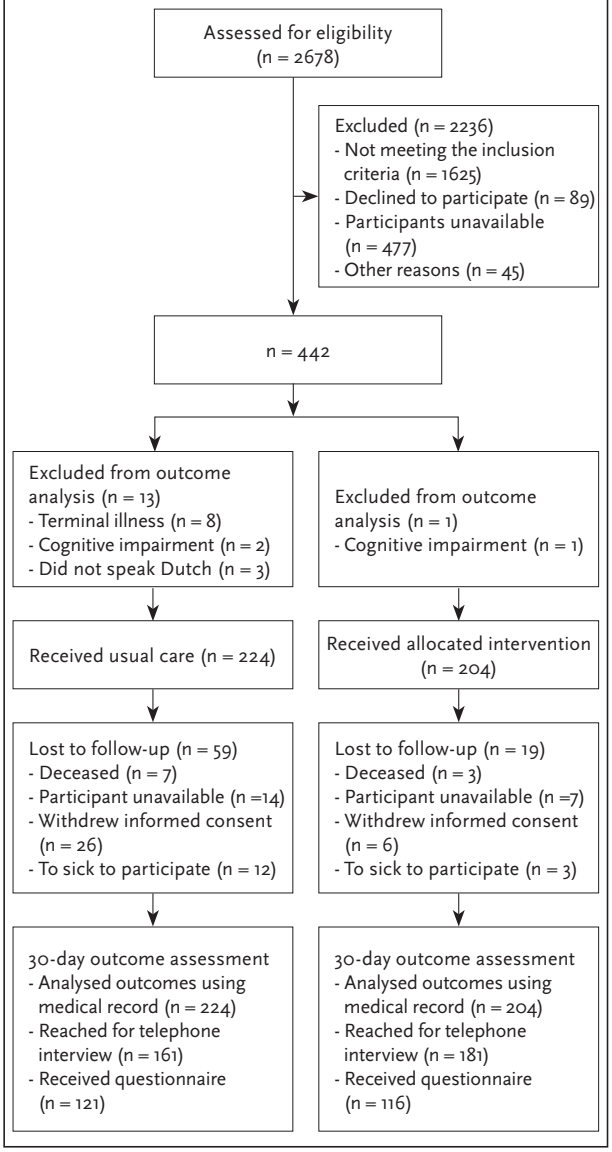

Table 1. *Baseline characteristics of the study population*

Characteristics	Pre-test n (%)	Post-test n (%)	P value[1]
Patients, n	224	204	
Age, mean (SD), years	55 (17)	58 (16)	0.20
Female, n (%)	101 (45)	95 (47)	0.77
Country of birth			0.01
- The Netherlands	136 (85)	123 (70)	
- Other	25 (15)	54 (30)	
Education level, n (%)			0.02
- Less than 6 classes of primary school	1 (1)	9 (5)	
- 6 primary school classes	9 (6)	17 (10)	
- More than primary school/ primary school with uncompleted further education	5 (3)	2 (1)	
- Practical training	18 (11)	23 (13)	
- Secondary vocational education	77 (48)	73 (42)	
- Pre-university education	11 (7)	23 (13)	
- University/higher professional education	39 (24)	29 (17)	
Social status, n (%)			0.70
- Alone	41 (25)	55 (31)	
- Living with partner	109 (67)	109 (62)	
- Other	12 (7)	13 (7)	
Living arrangement, n (%)			0.04
- Independent	159 (98)	166 (94)	
- Other	3 (2)	11 (6)	
Socio-economic status, mean (SD)[2]	-.1995 (1.24)	-.2208 (1.46)	0.87
Discharge diagnosis, n (%)			≤ 0.001
- Internal medicine	69 (31)	51 (26)	
- Infectious disease	32 (14)	35 (18)	
- Rheumatology	16 (7)	4 (2)	
- Disease of the digestive system	44 (20)	44 (23)	
- Chronic kidney disease	16 (7)	56 (29)	
- Malignancy	14 (6)	5 (3)	
- Cardiovascular disease	33 (15)	0 (0)	
CCI score, mean (SD)[3]	1.77 (1.95)	1.75 (1.56)	0.91
Readmitted ≤ 6 months before initial hospitalisation, n (%)	66 (30)	64 (31)	0.68
Length of index hospital stay, median (range)	6 (2-75)	7 (2-46)	0.04

Numbers in tables are n (%) unless otherwise indicated. SD = standard deviation. [1]Significant at p < 0.05. [2]Socio-economic scores (SES) of -1 < indicating low SES, > -1 and < 1 indicating medium SES, and 1 > indicating high SES. [3]Charlson Comorbidity Index (CCI) range of scores 0-31, 0 indicating no comorbidities, and 31 indicating presence of severe comorbidities.

without data on their healthcare utilisation and those without data on satisfaction with the discharge procedure between patients with complete and missing data on secondary outcomes.

Primary outcome after 30-days: readmission

No differences were present between the pre-test and post-test group in unplanned readmission rates within 30 days after discharge (12.9 vs. 13.2%, p = 0.93), as shown in *table 2*. Post-test patients had a trend toward a longer time to first readmission (10 vs. 14 days, p = 0.06). Logistic regression analysis, adjusted for covariates, showed that the odds ratio for readmission did not decrease for the post-test group (OR 1.28; 95% confidence interval 0.63-2.62). The self-reported readmission rate of patients was higher, but these also included planned readmissions.

Secondary outcomes: healthcare utilisation, mortality and patient satisfaction

More than half of all patients visited their GP and over 20% visited the emergency department in the post-discharge period, but no differences between the pre- and post-test groups were found (*table 2*). Mortality within 30 days after hospital discharge was only observed in the pre-test group and showed a trend towards significance compared with the post-test group (1.8 vs. 0.0%, p = 0.06). Overall satisfaction of the discharge process was high in both groups (7.5 vs. 7.4 points, p = 0.49). In the post-test period the medical discharge summaries were sent to the GP much faster than in the pre-test period (median of 5 days post-test vs. 14 days pre-test, p < 0.001).

In a subgroup analysis with patients hospitalised in the six months before study inclusion (index hospitalisation) we also found that the medical discharge letter was sent faster to the GP in the post-test group (14 vs. 5 days, p < 0.001) (*table 3*). Also in this high-risk group a trend to a decrease

Table 2. *Healthcare utilisation and patient satisfaction four weeks after hospital discharge*

Characteristics	Pre-test n (%)	Post-test n (%)	P value[1]
Patients, n	224	204	
Length of index hospital stay			
Length of index hospital stay, median (range)	6 (2-75)	7 (2-46)	0.04
Readmission			
Readmission within 30 days, % (n)	12.9 (29)	13.2 (27)	0.93
Time to first readmission, mean (SD)	10.4 (7.1)	14.2 (7.9)	0.06
Number of readmissions within 30 days, mean (SD)	0.19 (0.59)	0.19 (0.57)	0.99
Duration of first readmission, median (range)	4 (0-28)	1 (0-65)	0.52
Other healthcare utilisation			
GP visits, % (n)	52.8 (85)	59.0 (102)	0.26
ED visits, % (n)	24.9 (43)	21.0 (38)	0.39
Mortality within 30 days			
Died, % (n)	1.8 (4)	0 (0)	0.06
Patient satisfaction with discharge procedure			
Overall patient satisfaction, mean (SD)	7.5 (1.4)	7.4 (1.5)	0.49
Medical discharge letter in days, median (range)	14 (0-182)	5 (0-248)	<0.001

Numbers in tables are n (%) unless otherwise indicated. CI = confidence interval; SD = standard deviation; GP = general practitioner; ED = emergency department. [1]Significant at p < 0.05.

Table 3. *Analysis in 'high-risk group': patients who were admitted to the hospital in the six months prior to the index hospital stay*

Characteristics	Pre-test n (%)	Post-test n (%)	P value[1]
Patients, n	66	64	
Readmission			
Readmission within 30 days, % (n)	18.2 (12)	18.8 (12)	0.93
Time to first readmission , mean (SD)	8.5 (6.0)	12.5 (8.3)	0.22
Number of readmissions within 30 days, mean (SD)	0.26 (0.62)	0.31 (0.77)	0.66
Duration of first readmission, median (range)	3 (0-23)	1 (0-65)	0.42
Other healthcare utilisation			
GP visits, % (n)	52.4 (22)	59.3 (32)	0.50
Emergency department visits, % (n)	32.7 (16)	25.9 (15)	0.44
Mortality within 30 days			
Died, % (n)	4.7 (3)	(0)	0.08
Patient satisfaction with discharge procedure			
Overall patient satisfaction, mean (SD)	7.6 (1.1)	7.1 (1.8)	0.10
Medical discharge letter in days, median (range)	14 (0-182)	5 (0-78)	<0.001

Numbers in tables are n (%) unless otherwise indicated. SD = standard deviation. [1]Significant at p < 0.05.

in mortality within 30 days was seen after the intervention period (3 vs. 0%, p = 0.08).

Adherence to the discharge bundle

Patients self-report on the number of topics that were covered during verbal patient education showed some improvements, but no significant differences were seen between the pre- and post-test groups, respectively: diagnosis (80 vs. 80%, p = 0.91), pain management (61 vs. 76%, p = 0.10), post-discharge care (47 vs. 59%, p = 0.14), warning signs (46 vs. 59%, p = 0.13) and medication reconciliation (60 vs. 75%, p = 0.15).

Process indicators (all started at 0% before the intervention) showed that discharge planning within 48 hours after hospital admission was performed in 67% (range 0-100%), over a period of 33 weeks during the intervention period. Nurses completed the discharge checklist in 76% (range 53-100%) and residents in 10% (range 0-43%). The personalised patient discharge letter (35%, range 0-71%) and verbal patient education (33%, range 0-80%) were provided to patients before hospital discharge.

DISCUSSION

In this pre-post-test design study we did not find that implementation of a comprehensive discharge bundle was associated with a reduction of unplanned hospital readmission within 30 days after discharge and an increase in patient satisfaction on the overall discharge process. However, we observed trends to longer time to readmission and lower mortality rate in the post-test group. In addition, the intervention was successful in reducing time until sending the medical discharge summary to the GP after hospital discharge, which might contribute to effective communication and information transfer with the GP and patient safety.[7,8,29] The discharge bundle consisted of planning the date of discharge, a discharge checklist, a personalised patient discharge letter, and patient education.

Our findings are inconsistent with other reports[14,18,30] describing a decrease of hospital readmission rates. This might be due to several reasons. Adherence to some components of the discharge bundle was low. While compliance to the discharge bundle among nurses was satisfactory, compliance of residents to the checklist was poor. A possible explanation for this could be the staff rotation system. Every six months a new group of residents started and had to be trained about the discharge bundle. In the period just after they started, the adherence to the discharge bundle was low. Studies about influences on doctors' behaviour conclude that a combination of successful methods, such as education, feedback, participation, administrative interventions, and financial incentives and penalties, could change doctors' behaviour and contribute to the patient safety climate.[31] We used a multidisciplinary multifaceted implementation strategy[32,33] consisting of these methods. Some researchers[24,34] have also found differences in compliance by nurses and doctors and suggest that different dissemination and implementation strategies are needed for generating compliance by different disciplines. Furthermore, residents and nurses were not tested on a regular basis by the management on their performance of the elements of the discharge bundle, except the personalised patient discharge letter, which might have led to a decrease of commitment and sense of urgency.[24,35,36] Future studies should adjust implementation strategies to the specific needs of participating disciplines.

Implementation of the personalised patient discharge letter, which was a plain language handover consisting of personalised information about different relevant topics, was relatively successful. The writing of this letter was structurally implemented in the medical students' Masters education program and the quality and number was examined during their internship. We hypothesise that the top-down approach, its fast electronic sending to the GP, and the examination of the personalised patient discharge letter was the reason for the successful implementation and also the faster sending of the medical discharge letter by the residents.

We included all adult medical patients who were hospitalised for more than 48 hours, which might explain the unexpected lower rate of unplanned readmissions of about 13%, compared with others who found readmission rates as high as 39% in older people or those admitted with COPD or heart failure.[37] However, in our group of high-risk patients, defined as patients who were hospitalised in the six months prior to the index admission, we found a readmission rate of 19%. Presumably, only this high-risk group of patients may specifically benefit from a multicomponent intervention targeted at reduction of hospital readmission.[13,38,39]

The strength of this study is that the discharge bundle consists of several multidisciplinary interventions and demonstrates a positive trend toward longer time until readmission and a reduction in mortality. Furthermore, the effect and adherence to the discharge bundle was measured in several ways and at several moments.

Our study has some limitations; the first concerns the relatively short duration of the follow-up period. We selected a 30-day follow-up interval based on previous studies suggesting that patients are at highest risk for adverse events in the first 30 days after hospital discharge.[27] Other studies[40] used a follow-up period of three months

to indicate the effect of interventions on patient-related outcomes. Our study might have underestimated the effect of mortality due to the restricted follow-up period.
A second limitation, due to the restricted time period of this quality improvement project, was that we could only include a certain number of patients and did not perform a sample size calculation in advance. Since we had a low rate of readmissions in the pre-test group the room for improvement was lower than expected.

CONCLUSION

In summary we conclude that the comprehensive discharge bundle was not effective in reducing the 30-day readmission rate and increasing patient satisfaction, but medical discharge summaries were sent faster to the GP and a trend to a longer time to readmission and lower mortality rate was present in the post-test group.
Future research should focus on adjusting implementation strategies to the specific needs of participating disciplines and is warranted for improvement strategies concerning the discharge process outside the hospital.

ACKNOWLEDGEMENTS

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DISCLOSURES

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CASE REPORT

Mast cell leukaemia presenting with multiple osteoporotic fractures in an elderly woman

S.E. de Boer[1], K. Hoogenberg[2], N.K. de Boer[3]*

[1]Department of Internal Medicine, Deventer Hospital, Deventer, the Netherlands, formerly: Department of Internal Medicine, Martini Hospital, Groningen, the Netherlands; Department of [2]Internal Medicine and [3]Pathology, Martini Hospital, Groningen, the Netherlands, *corresponding author: tel.: + 31(0)50-524 6750, e-mail: n.k.deboer@mzh.nl

ABSTRACT

Osteoporotic fractures in elderly women are mainly due to postmenopausal bone loss but can sometimes be caused by a disabling haematological disease. We describe an 84-year-old woman suffering from multiple osteoporotic fractures as a manifestation of mast cell leukaemia. Mast cell leukaemia is a rare form of systemic mastocytosis with a poor prognosis and very few therapeutic options. Osteoporotic fractures have seldom been reported as its initial manifestation.

KEYWORDS

Secondary osteoporosis, vertebral fractures, mastocytosis, mast cell leukaemia

What was known about this topic?
Systemic mastocytosis is a rare disease of which a mast cell leukaemia is seldom seen. It results from a clonal proliferation and an accumulation of pathological mast cells in bone marrow and / or other extracutaneous tissues. Systemic mastocytosis frequently leads to osteoporosis because of the devastating effects that the mast cell mediators, such as histamine, heparin and cytokines (TNF, IL-6, TGF-beta), exert on bone turnover.

What does this add?
This is the first recorded case in which progressive vertebral fractures were the presenting symptom of mast cell leukaemia in a postmenopausal woman; the diagnosis could have been made earlier if many characteristic symptoms of mast cell disease had been recognised. Recognition of these symptoms is essential for specific diagnostic testing as these are not part of the general screening for secondary causes of osteoporosis.

INTRODUCTION

Osteoporosis is a common disease in postmenopausal women affecting approximately one-fifth of elderly women. It is characterised by a low bone mass and skeletal fragility, coupled with an increased fracture risk.[1] Osteoporotic fractures directly impair mobility and quality of life. In the majority of ageing women osteoporotic bone loss is related to oestrogen deficiency and advanced age, denoted as primary osteoporosis. In contrast, secondary osteoporosis may arise at any age and equally affects both men and women. This form results from several well-identified chronic predisposing disorders such as hypogonadism, gastrointestinal, haematological and rheumatological diseases, or prolonged use of medications such as glucocorticoids.[2] A secondary cause of osteoporosis can be identified in about 20-30% of postmenopausal women and 50% of men. In this report we describe a rare cause of secondary osteoporosis in an elderly woman with multiple osteoporotic fractures.

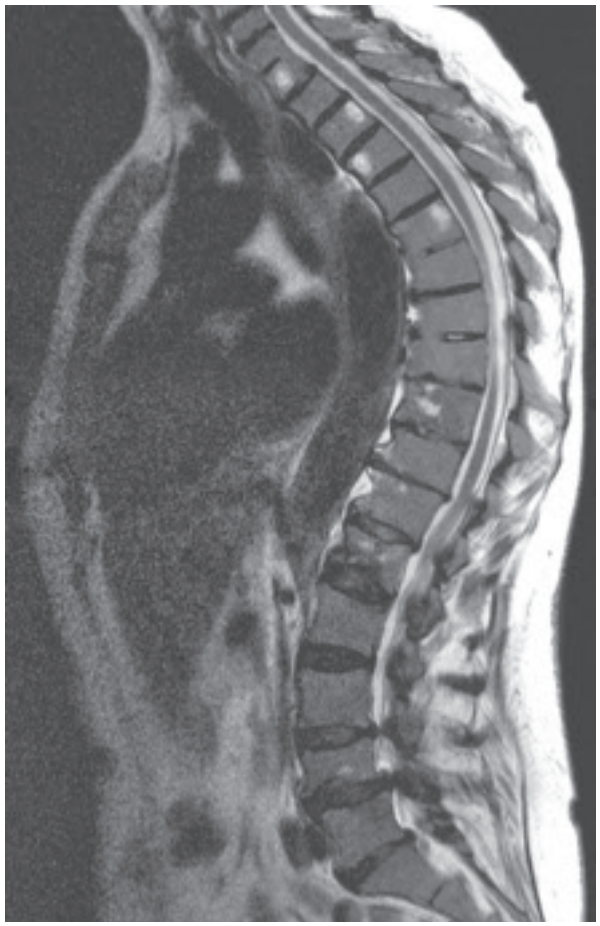
CASE REPORT

An 84-year-old woman with a vertebral fracture, caused six months earlier, which had been attributed to postmenopausal osteoporosis, was referred because

of disabling back pain after passing over a speed bump during a car ride. She had been feeling ill for quite some time, complaining of weight loss, loss of appetite, and clamminess at night. Her medication consisted of alendronate 70 mg once weekly, calcium-cholecalciferol 1.25 g/800 IU once daily and salmeterol/fluticasone inhalations. Her medical history revealed an urticarial rash to diclofenac. She had also been hospitalised recently as a result of hypotension attributed to systemic inflammatory response syndrome (SIRS), caused by a urinary tract infection. That admission was complicated by an episode of wheezing and dyspnoea ascribed to a COPD attack and an urticarial rash that was considered to be a reaction to antibiotics.

Upon physical examination, there were no overt abnormalities. Notably, the liver and the spleen were not enlarged and skin lesions were absent. Laboratory testing showed a normocytic anaemia (haemoglobin level of 6.8 mmol/l), leucocytes of 12.9 x 10^9/l with 10% large atypical cells, 1% erythroblasts and thrombocytes of 181 x 10^9/l.

Figure 1. *T2 weighted lateral MRI imaging showing compression fractures of the T10, L1 and L4 vertebrae with oedema around Th. 10 and L1, indicating that these are recent fractures*

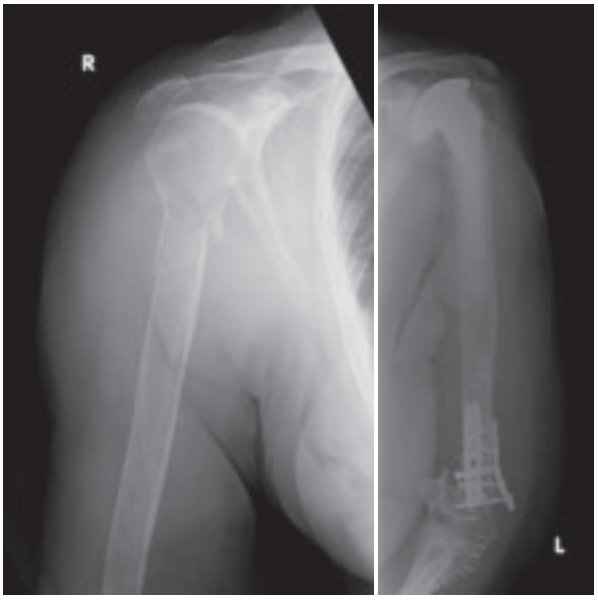


The erythrocyte sedimentation rate was 44 mm in the first hour, and the C-reactive protein was 6 mg/l. Kidney, liver and thyroid function, vitamins (cholecalciferol, folic acid and cobalamin), ferritin, iron parameters, calcium and albumin were all within normal ranges. A lumbar X-ray showed fractures of L1, L4 and Th10. An MRI performed later showed that the L1 and Th10 fractures were recent (*figure 1*).

A diagnostic procedure was started to search for secondary causes of osteoporosis, such as metastatic bone, or a primary haematological disease. A bone scintigraphy showed abnormalities of the lumbar spine, the right iliac crest and several ribs. These lesions were suspicious of metastatic bone disease on a CT scan. The diagnostic process was complicated by two consecutive pathological fractures of the right and left humerus (*figure 2*) that developed during nursing and for which she was operated. Both operations were complicated by hypotension which was ascribed to SIRS for which she was treated with antibiotics.

A bone marrow aspirate and biopsy were taken from the right ileac crest, of which the aspirate was hypercellular with an increase in megakaryocytes with dysplastic maturation features, and a decrease in the erythroid, lymphoid and myeloid lineage cells without distinct dysplasia. There was a diffuse infiltration of more than 50% large polymorphic cells. The bone marrow biopsy showed similar abnormalities with the presence of many atypical cells. In addition the biopsy showed thin, broken

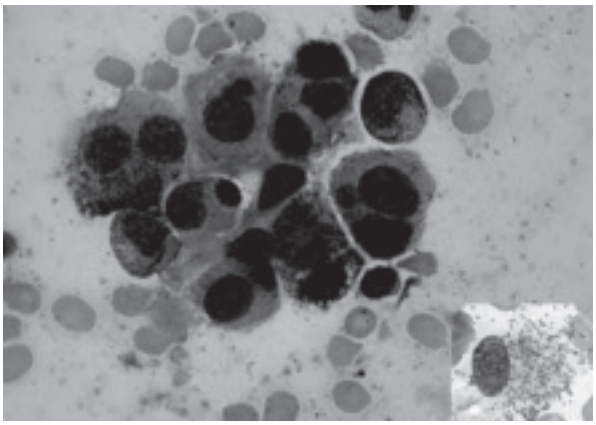
Figure 2. *Subcapital right humerus fracture (left panel) and supracondylar left humerus fracture after osteosynthesis (right panel) in the patient developed during daily nursing*



trabeculae and focal bone formation. Immunohistological staining showed that the atypical cells were CD117 positive. They were recognised as atypical mast cells (*figure 3*). A later serum tryptase level was extremely high: 1040 µg/l (normal values < 11.4 µg/l). A genetic D816V mutation could not be detected. The diagnosis was established to be a systemic aggressive mastocytosis and because of the number of mast cells, mast cell leukaemia. These cells were also seen in the peripheral blood smear.

The patient was given symptomatic treatment through sodium cromoglycate and high-dose H1 and H2 antagonists. She was also put on teriparitide injections and mast-cell eradication therapy through imatinib. Despite these treatments her disease continued to cause complications. Over the next few weeks, she was hospitalised four times for hypotension associated with dyspnoea, wheezing and pulmonary oedema. Initially, each time her symptoms were attributed to SIRS. Later, they were correctly denoted to be anaphylactic reactions through massive mast cell degranulation, caused by her mast cell leukaemia. At the last admission her hypotensive shock was refractory and respecting the policy of no resuscitation, she died one day later.

Figure 3. *Bone-marrow smear (May-Grunwald Giemsa stained, x100) of the patient showing that 50% of the cells are mast cells ranging from mature mast cells to immature promastocytes and blasts. The mast cells show cytological abnormalities, such as cell enlargement, the presence of multilobulated nuclei and focal granule accumulations. Immunohistological evaluation of the biopsy showed that the cells were CD117 positive. A normal mast cell is shown on the bottom right*



DISCUSSION

Mastocytosis comprises a rare group of disorders which are characterised by a clonal proliferation and an accumulation of pathological mast cells. Mastocytosis can be either limited to the skin (cutaneous mastocytosis), or it can involve bone marrow and other extracutaneous tissues such as the spleen, lymph nodes, liver and gastrointestinal tract (systemic mastocytosis).[3,4] The systemic findings and symptoms are due to mediator release by the mast cells (of which histamine is the most important) and organ infiltration. These can lead to angioedema, flushing, nausea, vomiting, abdominal pain, diarrhoea, unexplained syncope and pulmonary oedema (anaphylactic attacks), hypersplenism, osseous pain, or pathological fractures.[3,4] Most of these symptoms were prominent in our patient.

Systemic mastocytosis can be classified as indolent, aggressive, associated with a clonal non-mast cell lineage disease, and mast cell leukaemia. The classification depends on the results of the bone marrow biopsy and associated findings.[4] In mast cell leukaemia, the percentage of mast cells is ≥ 20% in bone marrow aspirate.[4,5] It was remarkable that the massive bone marrow infiltration did not result in a pancytopenia in our patient.

A number of clinical conditions may lead to the suspicion of systemic mastocytosis, such as unexplained anaphylaxis (as in our patient), severe osteoporosis of unknown aetiology (as in our patient), unexplained neurological or constitutional symptoms, unexplained ulcerative intestinal disease or chronic diarrhoea.[3,4] Many of these conditions were present in our patient, although they were initially not recognised as the histamine effects on H1 and H2 receptors resulting in vasodilatation and increased vascular permeability. Instead, the symptoms were several times mistakenly interpreted as SIRS, even after the patient had been diagnosed with mast cell leukaemia.

Mast cell leukaemia is a very rare form of aggressive systemic mastocytosis accounting for < 1% of all mastocytosis. It may appear de novo or secondary to previous mastocytosis.[5] Cytotoxic therapy with cladribine, interferon-α and imatinib have been used with poor results with a median survival of seven months, with patients dying between 2-29 months from progression or multiorgan failure.[5] Current therapy in systemic mastocytosis is largely palliative and directed at diminishing the symptoms of mast cell degranulation and/or organ dysfunction from mast cell tissue infiltration.[4]

Half of all adult patients with systemic mastocytosis have bone involvement with osteoporosis as the most common manifestation. An osteoporotic fracture is the presenting symptom in only a small minority of patients.[6] Osteoporosis in systemic mastocytosis is due to the direct effects on bone turnover of the mast cell mediators histamine, heparin and the cytokines TNF, IL-6, and TGF-beta.[7] In our patient, it was initially justified to attribute her vertebral fractures to primary osteoporosis. Osteoporosis guidelines recommend searching for secondary causes by measuring erythrocyte sedimentation rate, calcium, albumin, creatinine, thyroid-stimulating

hormone, 25(OH)D and alkaline phosphatase. Serum protein electrophoresis, coeliac serology and parathyroid hormone need to be done on indication.[8] However, none of these investigations would have led to the diagnosis of systemic mastocytosis in our patient. It was the two new vertebral fractures that eventually led to the diagnosis of a mast cell leukaemia.

Most patients in whom an osteoporotic fracture led to diagnosis of systemic mastocytosis were younger and the majority were male.[9-14] There are three cases in which systemic mastocytosis was diagnosed during the primary evaluation of an osteoporosis.[9,11,14] There is also one case of an elderly woman with a previous osteoporotic fracture in whom systemic mastocytosis was established after a wasp sting induced an anaphylactic shock.[12] Hence, an osteoporotic fracture as a leading symptom to the recognition and diagnosis of systemic mastocytosis is rare. In case of the rarity of a mast cell leukaemia; there are only two cases reported in which pathological vertebral fractures revealed the diagnosis.[15,16]

In conclusion, we report a rare cause of secondary osteoporosis: mast cell leukaemia. A diagnosis that, retrospectively, could have been recognised earlier because of the many characteristic manifestations of mast cell disease. This is the first recorded case in which progressive vertebral fractures were the presenting symptom of mast cell leukaemia in a postmenopausal woman who had previously been diagnosed with primary osteoporosis. Despite its low prevalence, mastocytosis should be included in the differential diagnosis of severe osteoporosis, especially when associated with symptoms of mast cell mediator release.

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DISCLOSURE

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PHOTO QUIZ

Skin lesions in a patient with multiple myeloma

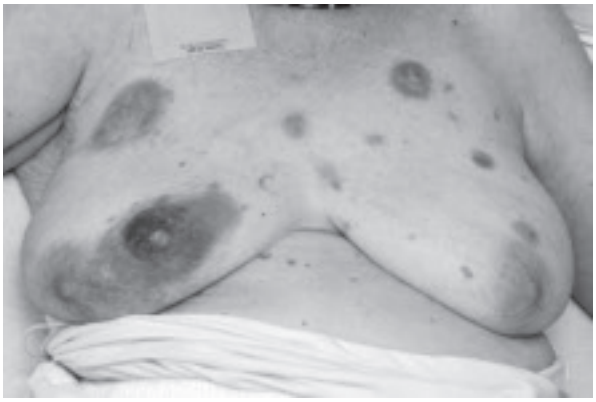
M. Mebius[1]*, M. Westerman[2], C.H. Smorenburg[3]

[1]Department of Internal Medicine, Rijnland Hospital, Leiderdorp, the Netherlands, [2]Department of Haematology, Medical Centre Alkmaar, Alkmaar, the Netherlands, [3]Department of Medical Oncology, Antoni van Leeuwenhoek, Amsterdam, the Netherlands, *corresponding author: e-mail: m.mebius@rijnland.nl

CASE REPORT

A 78-year-old woman presented at our outpatient clinic with multiple nodules on her breasts (*figure 1*). The lesions spread slowly and were firm and non-tender. Fifteen years ago she was diagnosed with multiple myeloma (IgG kappa, Durie-Salmon stage II) which was successfully treated with high-dose melphalan and autologous stem cell transplantation. However, she had recurrent disease for the last seven years and was subsequently treated with melphalan-prednisone, thalidomide, bortezomib and lenalidomide. Physical examination revealed no other abnormalities. Laboratory tests showed a normal level of calcium, renal insufficiency (glomerular filtration rate 35 ml/min), anaemia (haemoglobin count 6.3 mmol/l) and an IgG kappa paraprotein of 20 g/l. X-ray examinations showed osteolytic bone lesions in the radius, humerus, femur and tibia.

Figure 1. *Metastatic skin lesions*



WHAT IS YOUR DIAGNOSIS?

See page 334 for the answer of this photo quiz.

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PHOTO QUIZ

The zebra among horses: extensive abnormalities in a kidney biopsy without clinical signs of kidney disease

M.J.S. Oosterveld[1]*, S. Florquin[2], M. van den Bergh Weerman[2], L. Vogt[3]

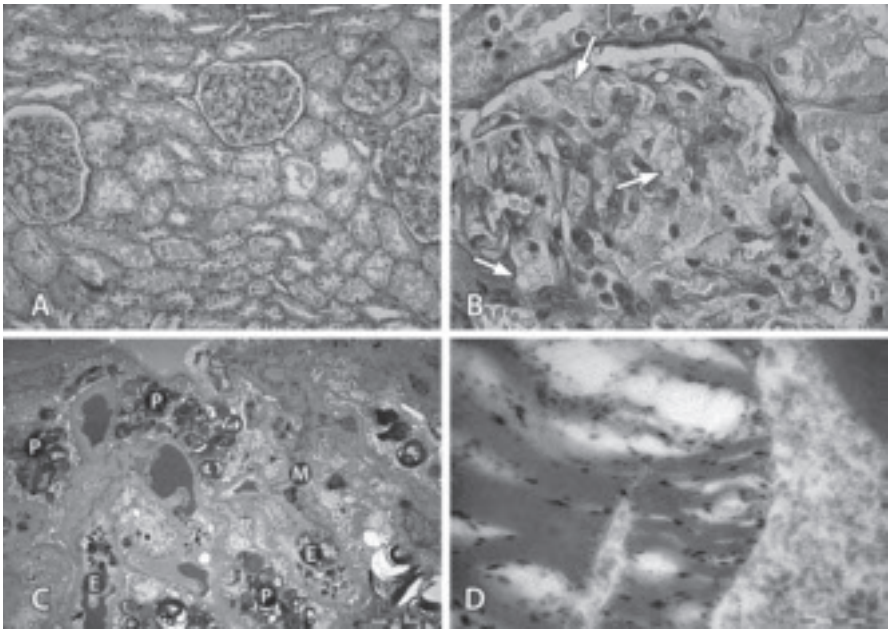
Departments of [1]Pediatric Nephrology, [2]Pathology and [3]Nephrology, Academic Medical Center, Amsterdam, the Netherlands, *corresponding author: tel: +31 20 566 8844, fax: +31 20 566 9683, e-mail: m.oosterveld@amc.nl

A 13-year-old boy presented to the outpatient clinic with a 4-5 year history of cramping pains in the hands and feet. The reported pains were so severe as to force him to lie down and, on occasions, vomit. The pains were intermittent in nature and more common during warm weather and on physical exertion. The patient was well apart from a history of migraines and a period of macroscopic haematuria diagnosed as post-streptococcal glomerulonephritis five years ago. Physical examination revealed some angiokeratomas on the face, thorax and arms. Blood pressure was 112/80 mmHg. Urinalysis (dipstick) was negative, no proteinuria was present (albuminuria < 3 mg/day) and kidney function was normal (serum creatinine 48 μmol/l, estimated glomerular filtration rate 128 ml/min/1.73m^2 (Schwartz formula)). Based on a Google search, the boy's parents suspected Fabry's disease. Cardiac ultrasound, MR brain and audiology testing were normal. Ophthalmoscopy revealed cornea verticillata. A kidney biopsy was performed.

WHAT IS YOUR DIAGNOSIS?

See page 335 for the answer of this photo quiz.

Figure 1. *A) Low magnification of the periodic acid Schiff staining showing no overt pathological changes, magnification x 10; B) High magnification of the periodic acid Schiff staining showing extensive vacuolisation of the podocytes (arrow), magnification x 40; C) Electron microscopy of one glomerulus showing lamellar structures in the cytoplasm of podocytes (P), endothelial cells (E), and mesangial cells (M); D) Electron microscopy at high magnification showing classical zebra bodies*



Netherlands
The Journal of Medicine

PHOTO QUIZ

An unusual peripheral blood smear

S.H. de Hoog*, W.L. Blok, M.L. van Ogtrop, G.E.L. van den Berk

Department of Internal Medicine and Medical Microbiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-5993503, fax: +31 (020)-5993523, e-mail s.h.dehoog@olvg.nl

A 27-year-old man from Ghana was referred to our hospital with a three-week history of fever, persistent cough and night sweats. He also reported the presence of blood in his sputum and a 20 kg weight loss. His medical history was unremarkable. He had been living in the Netherlands since 2004, working as a cleaner.

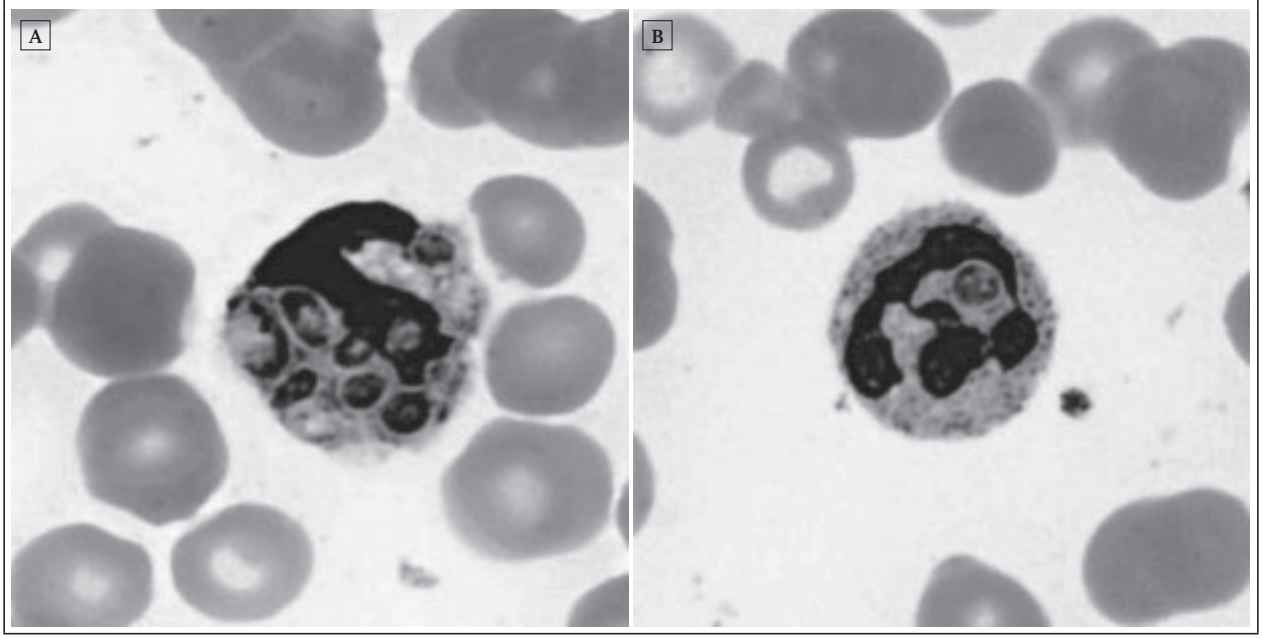
On admission his physical examination showed a blood pressure of 110/65 mmHg with a pulse of 130 beats/min and a temperature of 39.3 °C. There were multiple small lymph nodes (bilateral submandibular and inguinal); further physical examination revealed no abnormalities.

Laboratory results showed a haemoglobin of 4.7 mmol/l, mean cell volume 67.4, leucocytes 1.2 x 10^9/l, ferritin 69.401 µg/l and lactate dehydrogenase of 2967 U/l. The chest X-ray was unremarkable. Two hours after presentation the laboratory calls to report an abnormal blood smear (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 336 for the answer of this photo quiz.

Figure 1. *[Auteur: graag figuurtitel toevoegen]*



Netherlands
The Journal of Medicine

PHOTO QUIZ

Haemorrhagic shock and spontaneous haemothorax

J. Heidt[1,*], X.Y.D Beele[2], K.P. van Lienden[3], R. van Raalte[1]

[1]Department of Intensive Care, Tergooi Hospital, Hilversum, the Netherlands, [2]Department of Radiology, Tergooi Hospital, Hilversum, the Netherlands, [3]Department of Interventional Radiology, Academic Medical Centre, Amsterdam, the Netherlands, *corresponding author: tel.: +31(0)88-7531753, fax: +31(0)88-7531289, e-mail: jheidt@tergooi.nl

CASE REPORT

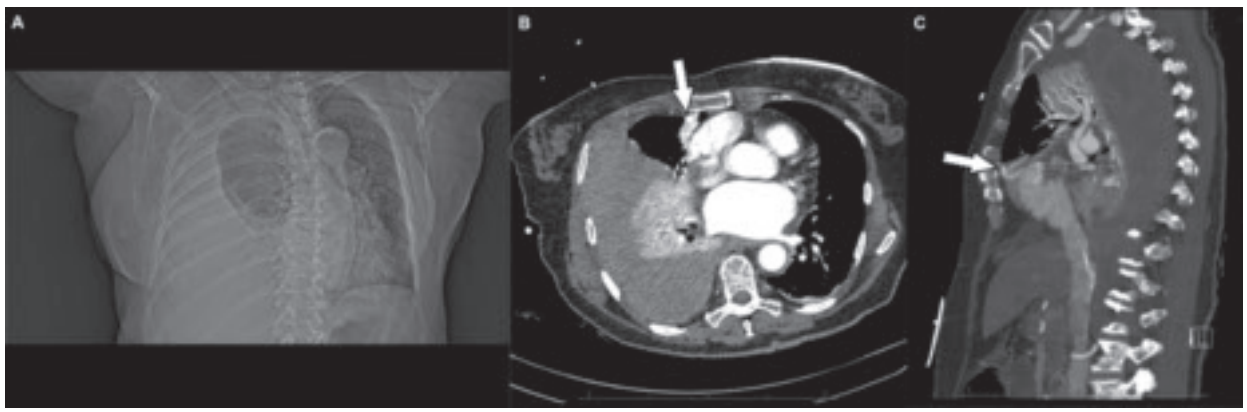
A 75-year-old female presented to the emergency department with dyspnoea, pain between the scapulae and hypotension. She had no remarkable medical history and only used a non-steroidal anti-inflammatory drug for lower back pain. There was no recent history of cough, fever or haemoptysis.

Under suspicion of an aortic dissection she was transferred to the radiology department for a CT scan where she lost consciousness and developed pulseless electrical activity. Cardiopulmonary resuscitation (CPR) was initiated and due to right-sided diminished lung sounds and the suggestion of a tension haemo/pneumothorax on the preparation CT scan a needle thoracocentesis was performed, which drained blood. After ten minutes of CPR she regained spontaneous circulation. She was mechanically ventilated and transferred to the intensive care unit for further resuscitation. Laboratory results showed a decreased haemoglobin level of 3.7 mmol/l, a haemorrhagic coagulopathy (platelets 105 x 10^9/l, prothrombin time 24.8 seconds and an activated partial thromboplastin time of 82 seconds) and severe combined acidosis (pH 6.76, pO2 16.7 kPa, pCO2 8.2 kPa on 1.0 fraction of inspired oxygen, lactate 16.2 mmol/l). Transfusion and correction of the coagulopathy was carried out. A chest drain was placed, which produced blood. After stabilisation a second CT scan was performed (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 337 for the answer to this photo quiz.

Figure 1. *A) Preparation CT scan, prior to CPR and chest drain placement, showing extensive pleural fluid with compression of the right lung and mediastinal shift; B) Transverse view of a contrasted CT scan showing extensive haemothorax (pleural fluid with Houndsfield Units +55, compatible with blood) with compression of the right lung and mediastinal shift. In the collapsed middle lobe a hyperdense structure is visible (subpleural, parasternal right, arrow); C) Saggital reconstruction of a contrasted CT scan showing an extensive haemothorax with compression of the right lung. A hyperdense structure is visible (arrow)*



ANSWER TO PHOTO QUIZ (PAGE 330)

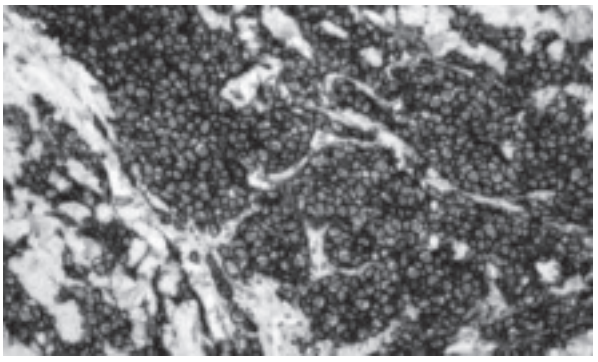
SKIN LESIONS IN A PATIENT WITH MULTIPLE MYELOMA

DIAGNOSIS

A skin biopsy was performed and immunohistochemistry revealed CD138 positive plasma cells (*figure 2*) with a similar expression of IgG immunoglobulin and light-chain kappa as identified in the serum of this patient.

Metastatic skin lesions in multiple myeloma are very rare and usually occur in patients with late stage disease. When these cutaneous metastases appear, the prognosis is poor with a reported survival of only a few months.[1,2] Despite palliative chemotherapy with cyclophosphamide every two weeks, which resulted in a partial response, our patient died of progressive disease four months after the occurrence of the skin lesions.

Figure 2. *Plasma cells in a skin biopsy*



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ANSWER TO PHOTO QUIZ (PAGE 331)

THE ZEBRA AMONG HORSES: EXTENSIVE ABNORMALITIES IN A KIDNEY BIOPSY WITHOUT CLINICAL SIGNS OF KIDNEY DISEASE

DIAGNOSIS

The kidney biopsy contained over 30 glomeruli without overt pathological changes at low magnification (*figure 1A*). At higher magnification, podocytes showed extensive but aspecific vacuolisation (*figure 1B*). Immunofluorescence was negative. At electron microscopy, massive accumulation of lamellated structures was present, not only in podocytes but also in endothelial cells, mesangial cells, parietal epithelial cells, fibroblasts and tubular epithelial cells (*figure 1C*). At higher magnification, 'zebra bodies' were seen (*figure 1D*) classical for Fabry's disease, an X-linked inborn error of the glycosphingolipid metabolic pathway. An alternative diagnosis would be renal phospholipidosis due to amphiphilic drugs (e.g. (hydroxy) chloroquine, amiodarone, gentamycin). The diagnosis was confirmed by mutational analysis and enzymatic testing of the leukocyte hydrolase alpha-galactosidase A (alpha-GalA) activity (< 0.5 nmol/h/mg protein (reference range 15-45)).

The clinical features of Fabry's disease result from lysosomal accumulation of globotriaosylceramide in a wide variety of cells. Neuropathic pains, predominantly in the limbs and precipitated by stress, extremes of heat or cold and physical exertion are characteristic for Fabry's disease and occur from a mean age of 10 years. Other symptoms of the disease tend to develop in the third and fourth decade and are rather nonspecific. These include telangiectasias and angiokeratomas, cardiac involvement (concentric left ventricular hypertrophy, heart failure), exercise intolerance, lymphadenopathy and gastrointestinal symptoms such as diarrhoea and abdominal pain. In view of the rarity of the disease, it is therefore understandable that a delay in diagnosis is common.[1]

Our patient did not have any of the renal symptoms reported in Fabry's disease (proteinuria, isosthenuria, Fanconi syndrome, decreased glomerular filtration rate or hypertension). Chronic kidney failure is common among untreated patients.[2] Affected males with very low levels of alpha-GalA activity, like our patient, tend to develop kidney failure from an earlier age.[2] Enzyme replacement therapy is reported to protect against progressive kidney function decline, and this might particularly be true when treatment is started early in the course of the disease.[3] For this reason a kidney biopsy was obtained despite the lack of renal symptoms. This case demonstrates that extensive kidney involvement of Fabry's disease might be present prior to clinical signs of kidney damage, e.g. microalbuminuria or decreased glomerular filtration rate.

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ANSWER TO PHOTO QUIZ (PAGE 332)

AN UNUSUAL PERIPHERAL BLOOD SMEAR

DIAGNOSIS/DISCUSSION

The differential diagnosis of this intracytoplasmic disease with systemic symptoms is very limited and should include Histoplasmosis/*Candida glabrata*/*Penicillium marneffei* and specific forms of *Trypanosoma cruzi*. Histoplasmosis was later confirmed by lymph node biopsy in Grocott methenamine silver stain. Since solitary histoplasmosis is very rare without an underlying condition we also suspected a human immunodeficiency virus (HIV) infection. The HIV test turned out to be positive with an absolute CD4+ count of 0 and a viral load of 5 million copies per millilitre.

Histoplasma capsulatum is a fungus and the aetiological agent of histoplasmosis. It is endemic in Africa, Asia and certain parts of North, Central and South America, especially in soil contaminated with bird or bat guano.[1] Infection follows after inhalation of the conidia where they reach the alveoli. There they are rapidly recognised and engulfed by resting alveolar macrophages. They subsequently transform into budding yeasts. In these cells the yeasts grow and spread to draining lymph nodes and further into the reticuloendothelial system. Most primary infections go unnoticed, because the yeasts are killed by activated macrophages and dendritic cells. This immune response takes approximately two weeks to develop. In immunosuppressed patients, however, the yeasts grow unchecked and most commonly spread to spleen, bone marrow and adrenal glands. Clinical manifestations consist of three types: pulmonary, disseminated and chronic cavitatory forms. Seventy percent of immunocompromised patients present with disseminated disease. Symptoms vary but consist of pulmonary symptoms, fever, weight loss and hepatosplenomegaly.

Diagnosis is made by a fungal culture but this can take up to one month and can be negative in less severe cases. Detection of histoplasma antigen in urine or blood is most sensitive.[2]

Treatment for disseminated disease consists of an induction phase with liposomal amphotericin B for approximately 2 weeks followed by maintenance for 12 months with itraconazole.[2,3] Antiretroviral treatment improves the outcome of disseminated histoplasmosis[4] and it is advised to start treatment promptly.

In our patient the diagnosis was confirmed with the blood smear and by lymph node biopsy. Furthermore, we ruled out tuberculosis and malignant lymphoma. We started liposomal amphotericin B 5 mg/kg for two weeks followed by itraconazole 200 mg twice a day and after two weeks we started him on highly active antiretroviral therapy. His condition gradually improved and two months after admission the patient was doing well and had resumed his job and daily activities.

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ANSWER TO PHOTO QUIZ (PAGE 333)

HAEMORRHAGIC SHOCK AND SPONTANEOUS HAEMOTHORAX

DIAGNOSIS

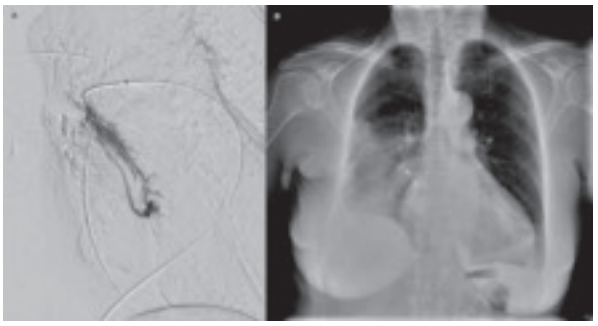
Causes of nontraumatic haemothorax include pneumothorax, coagulopathy, neoplasms, pleural endometriosis and vascular anomalies.[1] In our patient the CT scan revealed a haemothorax and a hyperdense structure matching a pulmonary arteriovenous malformation (PAVM).

PAVMs are abnormal connections between the pulmonary artery and vein, resulting in a low resistance right-to-left shunt. Most PAVMs are hereditary and occur in hereditary haemorrhagic telangiectasia, an uncommon autosomal dominant disorder associated with progressive development of vascular malformations. PAVMs may also be idiopathic, occur as a result of trauma and infection (e.g. schistozomiasis), or be secondary to hepatopulmonary syndrome in cirrhosis and bidirectional cavopulmonary shunting.[2,3]

Spontaneous haemothorax as a complication of a PAVM is rare and massive haemothorax with mediastinal shift has rarely been reported.[1,4] Incidence of haemothorax and haemoptysis in PAVMs varies from 1-8%.[5] Pregnant women are predisposed to rupture of a PAVM, especially in the last trimester. This is thought to be due to increased cardiac output and hormonal effects on the blood vessels, causing increase in size of the PAVM.[6]

The diagnostic tool of choice to determine the underlying cause of the haemothorax is multidetector CT angiography. Treatment of choice for PAVMs is transcatheter embolotherapy ('coiling'). If coiling is unsuccessful an exploratory thoracotomy should be performed.[3] One could argue immediate thoracocentesis with chest drains, as the haemothorax may tamponate the bleeding. Some authors suggest definitive thoracocentesis should be delayed until embolisation has been performed.[1] Our patient underwent a transcatheter embolisation and a video-assisted thoracoscopy for removal of the haematoma the day after (*figure 2*). No underlying cause for the PAVM could be found and she was diagnosed having an idiopathic PAVM.

Figure 2. *A) Image during angiography, showing the catheter positioned in the arterial feeder of the PAVM and outflow through the pulmonary vein. B) Chest X-ray, performed after the transcatheter embolisation and thoracoscopic removal of the haematoma*



Although rarely seen, a PAVM as underlying cause of a spontaneous haemothorax should always be considered. CT angiography is the investigation of choice to detect a PAVM.

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LETTER TO THE EDITOR

Caecal intubation rate in cases of colorectal cancer

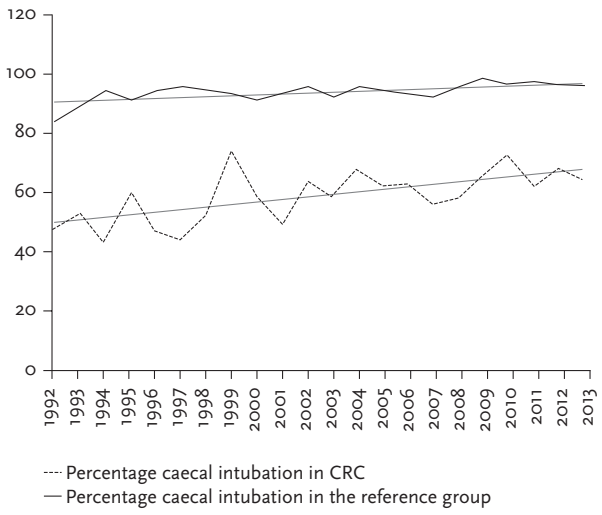
R.J.L.F. Loffeld*, B. Liberov , P.E.P. Dekkers

Department of Internal Medicine and Gastroenterology, Zaans Medical Centre, Zaandam, the Netherlands, *corresponding author: tel.: + 31 (0)75-6502779, fax: 31 (0)75-6502379, e-mail: Loffeld.r@zaansmc.nl

To the Editor,

Caecal intubation rate is a well-known quality indicator of colonoscopy. In the Netherlands all patients with colorectal cancer who undergo surgery are entered into a digital on-line system called the Dutch Surgical Audit on Colorectal Cancer.[1] According to the benchmark, in the report of 2012 preoperative inspection of the entire colon is recorded in 82% of cases (78% in case of colon cancer, 86% for rectal cancer). In normal daily practice this figure appears to be unrealistically high. It is not clear how the benchmark was established. For this reason we studied the caecal intubation rate in patients presenting with colorectal cancer. All consecutive patients undergoing colonoscopy, in whom colorectal cancer was seen, in the years 1992-2013, were included. Endoscopy was done after standard colon cleansing described in earlier papers.[2] Caecal intubation was recorded explicitly in all colonoscopies. All procedures were scheduled as colonoscopy. In other words, if caecal intubation was not successful the procedure was not renamed 'sigmoidoscopy'. All patients with no abnormalities served as a reference group. A total of 1336 patients with colorectal cancer were diagnosed (947 cases of colon cancer, 389 cases of rectal cancer). In 915 cases (68.4%) the caecum was successfully intubated: 688 (72.6%) cases of colon cancer, and 227 (58.3%) cases of rectal cancer. The reference group consisted of 6973 patients. In these cases the caecal intubation rate was 6586 (94.5%). Caecal intubation rate was significantly higher in the reference group ($p < 0.0001$). If rectal cancer and colon cancer were compared, the caecal intubation rate was significantly higher in cases of colon cancer ($p < 0.0001$). *Figure 1* shows the percentages of successful caecal intubation in patients with colorectal cancer and the reference group in the consecutive years. As can be seen in the trend line, the number of successful caecal intubations in patients with colorectal cancer rose over the years. The present study shows a lower caecal intubation rate than the benchmark used in the Dutch Surgical Colorectal Audit. Does this mean that quality of colonoscopy in the Endoscopy Department of the Zaans Medical Centre is low? The answer is no. For many years caecal intubation rates and the yield of colonoscopy have been recorded. Several studies have been published.[3,4] In the literature many reports are available of the caecal intubation rate; however, correction for case-mix has never been done. In a previous study reasons for not reaching the caecum were described.[5] In the consecutive years there was a clear trend towards a higher caecal intubation rate in cases of colorectal cancer. The main reason for this is probably a learning curve in the beginning of registration, but more

Figure 1. *The percentage of successful caecal intubation, with the trend lines, in patients with colorectal cancer and the reference group*



importantly, the introduction of newer, longer and stiffer endoscopes.

We can only speculate on the higher number of caecal intubations in the benchmark used in the Dutch Surgical Colorectal Audit. It is possible that the number in the benchmark is the result of an amalgamation of colonoscopy, virtual colonography or old fashioned barium enemas. Another explanation could be the use of the pilot studies on screening for colorectal cancer in the Netherlands. Obviously people who undergo screening should not have symptoms that can be the result of the condition for which the screening is done. It is possible that patients with colorectal cancer detected via the stool blood test and additional colonoscopy have smaller tumours not yet leading to symptoms and obstruction. Obviously, cancer can be obstructing. Although passage of stool is still possible, it may be impossible to introduce the endoscope above the level of the tumour. If the endoscopist persists in trying, because he wants to adhere to the benchmark, the chance of air entrapment is very high. Caecal blow-out is a well-known complication of endoscopy in case of a tumour that cannot be passed by the endoscope.[6,7] Of course, it is beyond discussion that the entire colon should be inspected. It can be concluded that the caecal intubation rate in daily practice is lower than the benchmark. Endoscopists and surgeons should no rely too heavily on benchmarks generated via auditing systems, especially if it is not clear how this benchmark was generated.

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The importance of correct QTc measurement in elderly patients treated with QT interval prolonging drugs

E.J.M. Schrijver*, P.W.B. Nanayakkara

Department of Internal Medicine, VU University Medical Center Amsterdam, the Netherlands,
*corresponding author: tel.: +031 (0)20-4444362, e-mail: ej.schrijver@vumc.nl

To the Editor,

We read with interest the recently published article by Kan *et al*.[1] In this review, the authors address the identification and management of drug-intoxicated patients who may be at risk for prolongation of the QT interval corrected for heart rate (QTc) and possible torsades de pointes (TdP). They recommend a stepwise approach that includes identifying which QTc interval-prolonging drugs are involved and if additional risk factors are present, correct determination of the QTc interval using the Hodges or Frederica formula, and when indicated initiating monitoring and treatment.

While this review focuses on the intoxicated patient, this is also very important in the hospitalised elderly patient. Elderly patients may be more vulnerable for drug-induced QTc prolongation and consequently at risk for TdP since the QTc interval is known to increase with age.[2,3] Additionally, they often have other risk factors for QTc interval prolongation present such as myocardial damage, polypharmacy (e.g. use of class Ia or III antiarrhythmic agents, and specific antidepressants), or electrolyte disturbances. Several safety concerns have been raised for use of QTc interval-prolonging drugs such as fluoroquinolones and antipsychotics in elderly patients.[2,4] The antipsychotic haloperidol, currently the treatment of choice for most delirium, may induce QTc prolongation.[5] With delirium prevalence rates of more than 30% in older general internal medicine patients,[6] treatment initiation with haloperidol or other antipsychotics known to prolong the QTc interval in elderly patients is daily practice for many physicians. To date, there is no accepted standard for risk assessment and monitoring of elderly patients subjected to drugs that may potentiate QTc prolongation and TdP.

We are currently conducting a multicentre double-blind placebo-controlled randomised clinical trial (The HARPOON study; NCT01530308) to study the effects of haloperidol prophylaxis (1 mg twice daily for a maximum of seven days) on delirium in hospitalised older patients (≥ 70 years of age). A 12-lead ECG will be performed at different protocolised time points during prophylactic treatment. Two observers will manually determine the QTc interval independently of each other according to method 1 (as described in figure 1 in the article by Kan et al.).[1] Also, automated versus manual QTc interval measurement will be compared, given that previous studies have shown that agreement between these methods is generally low.[7]

We would hereby like to emphasise the importance of accurate QTc measurement by valid methods in the large number of hospitalised elderly patients subjected to drugs with the potential to cause cardiac complications.

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The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

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