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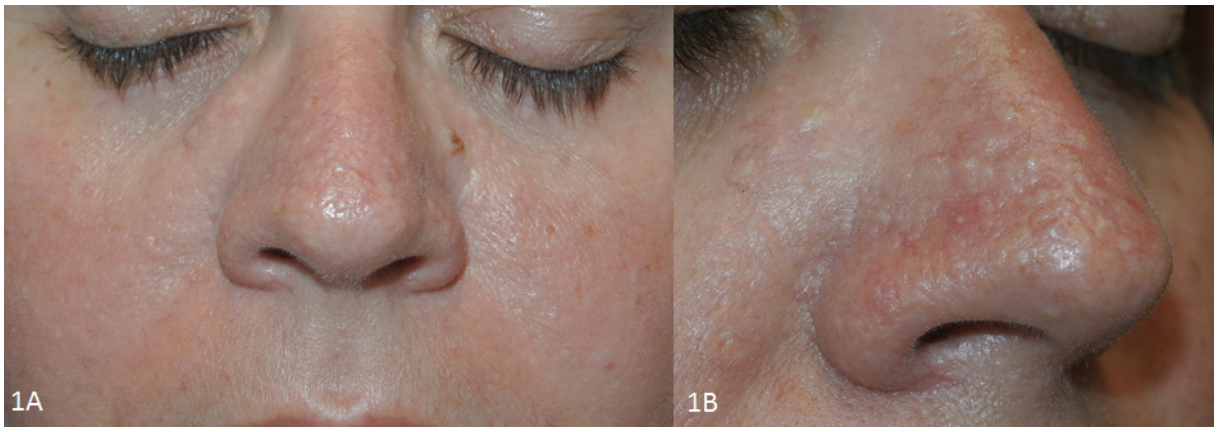

A lady with facial papules; what is your diagnosis?

Home haemodialysis in the Netherlands

SIRS, qSOFA or MEWS in sepsis

Androgenic steroid abuse and health problems

An alternative ICU staffing model

Q-fever awareness

May 2018, VOL. 76, NO. 4, ISSN 0300-2977

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The Netherlands Journal of Medicine

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EDITORIAL

Adverse effects of anabolic androgen steroid abuse in the Netherlands: Tip of the iceberg

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Endocrine advantages can have a major impact on sporting performance. This is exemplified by the story of legendary cross-country skier Eero 'Mister Seefeld' Mäntyranta (1937-2013) who had primary familial and congenital polycythaemia causing an increase in red blood cell mass and haemoglobin due to a mutation in the erythropoietin receptor gene. Other well-known examples include acromegalics who become successful bodybuilders or wrestlers (for example Jorge 'El Gigante' González [1966–2010]) or basketball players (Gheorghe 'Little Gheorghe' Mureșan [born 1971]). There are numerous examples of professional athletes without genetic variants or endocrine tumours who aimed to leverage the endocrine effects of doping to enhance their performance. However, this number is in stark contrast to the estimated 160,000 amateur athletes in the Netherlands who use performance enhancing drugs.[1] Because of this large number, the medical consequences and side effects of self-administration of mostly illegal doping treatments make this a relevant public health problem.

In the current issue of the Netherlands Journal of Medicine, Smit and de Ronde[2] focus on the estimated 20,000[1] amateur athletes that abuse anabolic androgen steroids (AAS), of which the tip of the iceberg was analysed in their one-of-a-kind outpatient AAS clinic. From their data, the average Dutch AAS abuser requiring medical aid due to AAS abuse is a 34-year-old employed male bodybuilder using testosterone and/or non-prednisolone derivate steroids and relatively likely to use recreational drugs such as XTC or cocaine. Interestingly, the results of the study show that the mostly self-derived or acquaintance-derived endocrine knowledge of AAS users can be very detailed. This is illustrated by combined self-medication regimens that include growth hormone, thyroid hormone, tamoxifen, human chorionic gonadotropin and/or clomiphene citrate. As a consequence, there is also very widespread endocrine-related symptomatology (including fatigue, decreased libido, gynaecomastia but also fluid retention and insomnia) and abnormal blood test patterns (including androgen deficiency, elevated creatine kinase, abnormal liver function tests and polycythaemia). Taken together, it seems evident that a specialised outpatient clinic is necessary in order to provide optimal care for these complex endocrinopathies that occur in such a heterogeneous group of patients. It can be challenging to set up good healthcare for medical issues that touch upon illegal substances or related to social outliers. The principles behind setting up a structured outpatient clinic for the consequences of AAS abuse fits with the progressive liberal mindset in the Netherlands. The same mindset has formed the basis for the successful medicalisation policies of heroin abuse in the 1970s and a frontrunner role in endocrine treatment of transsexual persons.[3,4]

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REVIEW

Home haemodialysis in the Netherlands: State of the art

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ABSTRACT

Home haemodialysis (HHD) has gained popularity in recent years, due to improved clinical outcomes associated with frequent or prolonged haemodialysis sessions, best achievable at home. However, several barriers to HHD are perceived by the physician and patient, among which lack of experience and education, logistic difficulties and reimbursement issues seem to be the most important ones. HHD, in particular when performed with intensified frequency or duration, is associated with improved quality of life, blood pressure control and survival. Serious adverse events are rare; however, more vascular access complications arise due to frequent needling. This emphasises the importance of comprehensive education and training. This review aims to provide the physician with a detailed state of the art overview on HHD in the Netherlands, discussing potential barriers and benefits, and offering practical advice.

KEYWORDS

Barriers, daily haemodialysis, education, home haemodialysis, nocturnal haemodialysis

INTRODUCTION

In 1961 home haemodialysis (HHD) was introduced by the Japanese doctor Yukihiko Nosé.[1] The reason to perform haemodialysis (HD) in this unorthodox environment was primarily a practical consideration, since a proportion of the patients with end-stage renal disease (ESRD) could not be offered in-centre chronic haemodialysis due to capacity problems. The first HHD session was performed by a domestic washing machine with a frame coil dialyser, hence reducing costs. In the early 1960s, HHD programs were initiated in Seattle, Boston and London, and the rest of the world followed shortly thereafter.[2] In the Netherlands, the first patient was treated with HHD in 1968.[3] In the early 1970s, 59% of the dialysis population in the United Kingdom and 32% in the USA received HHD. By the end of the 1970s the number of HHD patients reached its peak.[4] Prevalence in Australia and New Zealand was as high as 45%.[5] At that time, 10% of dialysis patients were treated with HHD in the Netherlands.[6] Due to several factors, HHD rapidly waned from practice in the 1980s and 1990s, although large variations between countries remained. Australia and New Zealand maintained the largest population of HHD patients (9% and 18%, respectively),[7] while prevalence of HHD in the USA declined to 2%[8] and some countries no longer offered HHD at all.[9] Reasons for the decrease in HHD in the Netherlands include the introduction of continuous ambulatory peritoneal dialysis in 1979,[10] the

increase of living kidney transplantation, the formation of satellite HD facilities, and eventually, lack of experience of nephrologists.[4,11]

Over the past decade, cumulative evidence demonstrated improved clinical outcomes with more frequent and/or prolonged (nocturnal) HD (in this paper designated by the term intensive HD), more easily provided in the home environment, compared with in-centre conventional HD (CHD). This, combined with the demand for reduction in healthcare costs, has led to a renewed interest in HHD. In the Netherlands, the number of HHD patients is steadily increasing from 112 (~2.0% of all dialysis patients) in 2006 to 273 patients (~4.2%) in 2016.[12] Probably, a lot more patients could benefit from this treatment modality. This narrative review aims to provide a thorough overview of current practices and literature on HHD.

PATIENT SELECTION, EDUCATION AND TRAINING

Patient selection

Whether a patient is suitable to perform HHD is largely dependent on patient motivation and the availability of family or medical staff support.[13,14] In fact, most of the patients requiring dialysis are medically suitable for HHD.[13,15,16] According to the National Institute for Health and Care Excellence (NICE), suitable candidates for HHD should be able and willing to learn the technique, be able to carry out the procedure (or be supported by a caregiver), be stable on dialysis, have suitable vascular access and have appropriate housing – after adaptations have been made – to accommodate the HD machine and equipment. Contraindications include severe intradialytic hypotension[17] and unstable behavioural problems.[17,18] The patient selection process, which includes providing information and a comprehensive assessment of the patient's healthcare needs and social circumstances including a home visit, should identify patients who are both physically and mentally able to perform HHD.

Patient education

The early identification of a potential HHD patient and timely initiation of patient education in the pre-dialysis period can help to overcome the barriers to HHD (see Barriers to home haemodialysis, later in this article). A comprehensive pre-dialysis education (CPE) program should provide patients and their family with clear and objective information on chronic kidney disease and the different treatment modalities, including kidney transplantation and conservative care. The program should promote self-care dialysis, use a multidisciplinary approach (nephrologist, dialysis nurse, dietician, psychologist, social worker), address psychosocial attitudes, misconceptions and fears, and promote shared-decision making. Of utmost importance is a dedicated team, with expertise in different treatment modalities. CPE programs meeting these criteria are successful in increasing the number of patients choosing home dialysis, including HHD, even after an urgent unplanned start of dialysis.[19-21] Shukla et al. reported on a successful CPE program in their clinic for future dialysis patients. The program required patients to attend a half-day at the clinic, starting with a whole-group session on kidney disease and renal replacement therapy options followed by individualised sessions with a dialysis nurse, a dietician, a social worker and the nephrologist. Patients were able to re-attend the program, yet almost 50% attended only one day prior to their first dialysis session. After multiple program meetings, the majority of 70% chose dialysis treatment at home: 55% chose peritoneal dialysis and 15% chose HHD.[21] After initiation of the CPE program the number of home dialysis patients more than doubled.

Patient training

Initial HHD patient training is performed by a few training facilities in the Netherlands, since a centralised program facilitates logistics and optimises clinical expertise.[22] The training comprises all aspects of HD, from preparation of the dialysis fluid to machine set-up, from access puncturing and access care to assessing dry weight, etc. The training program should train patients and family caregivers to act appropriately in case of acute events and instruct them to call the dialysis centre or hospital 24 hours a day for any acute problem. The training period generally lasts 6-12 weeks, subject to the patient's knowledge and skills.

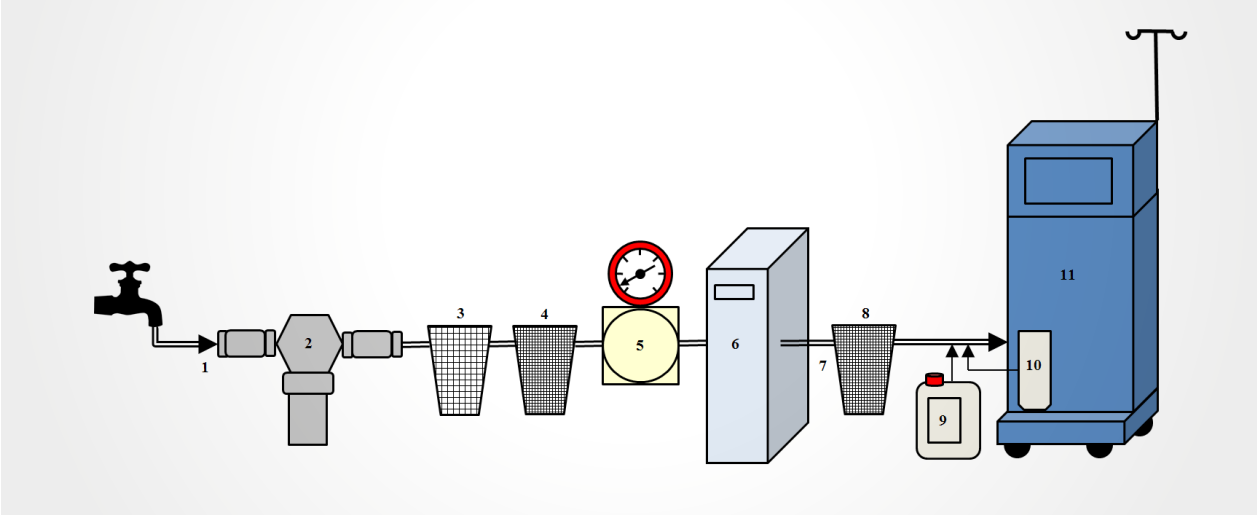
PRACTICAL AND TECHNICAL ISSUES

Not every house is suitable for HHD because it requires space, plumbing and electrical modifications to accommodate the dialysis machine, and will put higher demands on standard utilities and services.

Drinking water

The Water Supply Act in the Netherlands sets the standard for water used for drinking, cooking, and other domestic purposes.[23] With regard to public health, additional demands are imposed by the 'drinking water decree'.[24] The drinking water regulations establish the standards to be met by water supply companies concerning the design of facilities, control measures, and registration in logbooks.[25] The Dutch water supply companies are responsible for the delivery of drinking water that complies to the aforementioned obligations. Dutch drinking water is non-chlorinated and free of chloramines, in contrast to

Figure 1. *Standard water treatment system for HHD in the Netherlands. 1: drinking water, 2: backflow preventer, 3: 30-micron sediment filter, 4: 5-micron sediment filter, 5: pressure meter, 6: RO unit, 7: purified or RO water, 8: extra filter, 9: acid concentrate, 10: bicarbonate concentrate, 11: haemodialysis machine*



drinking water in many other countries where disinfection with chlorine is still utilised. Chlorine is harmful to reverse osmosis (RO) membranes in the dialysis machine, also chloramines are toxic to humans. In situations where dialysate was contaminated with chloramines, patients developed haemolytic anaemia and methaemoglobinemia.[26] If feed water contains chlorine and/or chloramines, an activated carbon filter is mandatory. Because of the non-chlorinated drinking water, activated carbon filters are not a standard feature in water treatment systems for HHD in the Netherlands.

Water treatment systems for HHD

Drinking water taken from the urban supply is not safe for use in HD. Drinking water enters the water treatment system through a backflow-preventing device (*figure 1*). This backflow preventer is installed to prevent pollution of the urban water supply infrastructure due to backflow of the domestic water system.[27]

The drawn water passes two coarse filters to remove particulate matter, first a 30-micron sediment filter, then a 5-micron sediment filter. Next, the filtered water may be softened by a softener to protect the reverse osmosis membrane (RO membrane) from calcium and magnesium. The hardness of Dutch drinking water is low. Softeners are thus optional in Dutch domestic water treatment systems. The need for a softener is merely determined by the specifications of the portable RO unit used. Dependent of the brand and type, portable reverse osmose units (RO units) require a water inlet pressure between 1.5 and 3.0 Bar. The water pressure in the Dutch urban water supply systems is sufficient to overcome the pressure reduction by the domestic water treatment system. A booster pump is therefore not a standard feature of the water treatment system at home. Under special circumstances, such as positioning of the water treatment system on the ceiling, a booster pump is needed to provide a water pressure sufficient for normal functioning of the RO unit. The filtered (and softened) feed water is led into the portable RO unit for removal of ions, microbiological contaminants (bacteria, endotoxins, viruses) and dissolved organic substrates.

Water leaving the RO unit is called purified or RO water. The RO water is transported to the dialysis machine by a domestic distribution ring adapted to the specific situation on-site. The RO water passes one or two extra filters depending on the specifications of the dialysis machine used, hereby achieving additional bacterial, viral and endotoxin retention. The purified water is further processed into dialysate by adding acid concentrate and bicarbonate. RO water and dialysate for HHD should meet quality standards equal to those specified for in-centre HD as set by The Dutch Federation of Nephrology (in line with the European Pharmacopoeia Commission (*table 1*)).

Table 1. *Microbiological requirements and endotoxin levels*

	Micro-organisms, cfu/ml	Endotoxin, IU/ml
Tap water	On average 100	Not specified
Purified water	< 100	< 0.25
Dialysate	< 100	< 0.25

Electrical requirements

The current electrical safety norms, NEN1010:2015, were specified by Academic Hospitals Instrumentation Management Working Group (WIBAZ) in October 2015. NEN1010:2015 was incorporated in the Dutch Building Decree, which entered into force on 23 December 2016. HD is assigned to group 2. Safe HHD thus requires an isolation transformer.

Dialysis machines

Basically, all types of commercially available dialysis machines are suitable for HHD. Differences in design, size, noise level, user interface, and total cost of ownership will guide organisations enabling HHD to opt for a specific brand and type of dialysis machine. Over the last decade, several transportable HD machines have been introduced. They all have a short set-up time with disposable cartridges and automatic priming. These machines have a compact cycler (± 40 x 40 x 45 cm) and make use of 5 litre lactate-based dialysate bags, or have the possibility to produce purified water themselves from the domestic water supply. Novel miniaturised HD machines are in development.

Quality control and maintenance

HHD quality control is organised in accordance with currently applicable clinical guidelines. Quality control includes calibration of the dialysis machine at home at the time of installation, quarterly examination of RO water and dialysate (on bacterial contamination and endotoxins), and a yearly check on the levels of organic and inorganic contaminants. Scheduled maintenance of water treatment systems and dialysis machines is mandatory.

Specific mutual arrangements with water supply companies are necessary. Water supply companies should be informed about patients on HHD in their region and need to inform enablers of HHD timely in case of work on the urban water supply system or increased concentrations of toxic substances, such as aluminium.

Logistics

HHD patients need scheduled home delivery of materials and prescriptions related to dialysis. As a rule of thumb patients receive a four-week delivery, meaning shipment of a trolley containing one and a half to two cubic meters of materials. The materials are to be stored in patients' homes including an additional two-week stock in case of unforeseen events. Most HHD providers strive for a single supplier situation to prevent frequent deliveries by third parties.

Monitoring of treatment and patients

Monitoring of patients during HHD is an ongoing challenge. So far, monitoring of HHD is based on completed paper records, video calls using available non-secure commercial applications, and/or visits to the outpatient clinic. Initiatives to develop encrypted (safe) IT solutions allowing online monitoring during HHD and video calling and storage of the visual material are eagerly awaited.

HOME HAEMODIALYSIS REGIMENS

The dose of dialysis delivered with CHD is often limited by the overall weekly treatment time and frequency. To deliver the minimum amount of adequate dialysis, CHD utilises high-efficiency dialysis over a short period of time. The resulting peaks and troughs of both hydration status and uraemic retention solute concentrations can lead to dramatic changes in the internal milieu. The home setting offers more flexibility of treatment schedule and facilitates intensive HD sessions, which are summarised in *table 2*.[28] Intensive HD regimens include short daily haemodialysis (SDHD), prolonged and prolonged-frequent HD. Prolonged (frequent) HD is usually performed during the night (nocturnal HD). Intensive HD can reduce the fluctuations of the internal environment by maintaining a more steady state, and by avoidance of a long interdialytic interval.[29]

Table 2. *Conventional and intensive haemodialysis regimens (Adopted from Chan CT et al.[28])*

	Conventional HD	SDHD (frequent)	Prolonged HD	Prolonged – frequent HD
Frequency (times/week)	3	5-6	3-4	5-6
Duration (hours/session)	4	2-3.5	> 5.5	> 5.5
Dialysate flow (ml/min)	500-800	500-800	300-500	300-500
Blood flow (ml/min)	300-400	400	200-400	200-300
Standardised Kt/V_{urea}	2.5 (12h/week)	3.75 (13.5h/week)	3.75 (26.8h/week)	5.82 (40.2h/week)

HD = haemodialysis; SDHD =short daily HD.

OUTCOMES OF HOME HAEMODIALYSIS

Patient survival

HHD has undergone a significant revival during the past 10 years.[30] Growing data supporting the association of intensive HD, most easily achieved in the home setting, with improved outcomes such as survival are the primary drivers for this resurgence. Most survival studies did not compare HHD versus in-centre HD, but intensive regimens (mostly performed at home) with a conventional (3x/week) regimen. Charra et al. reported a dramatic improvement in survival of dialysis patients in Tassin (France) by extending the length of HD sessions.[31] The survival benefit for patients undergoing nocturnal (NHD) and short-daily (SDHD) haemodialysis has been evaluated in a number of studies. Although no well-powered randomised controlled trial has been performed to date and the bulk of the data remain observational, the evidence points toward a better survival for patients receiving SDHD and NHD compared with those treated with conventional regimes.[32-41] A cohort study by Lacson et al. reported a mortality benefit for in-centre nocturnal HD (INHD) with a significant hazard ratio (HR) at both 1 year (HR 0.73, 95% CI 0.56-0.96, p = 0.02) and at 2 years (HR 0.75, 95% CI 0.61-0.91, p = 0.004) compared with a propensity-score-matched in-centre CHD arm.[40] Ok et al. also demonstrated a one-year survival advantage favouring INHD over CHD (HR 0.32, 95% CI 0.10-0.98, p = 0.04) after adjusting for age, gender, dialysis vintage, and the presence of diabetes.[41] In a study of prevalent Canadian patients, Pauly et al. reported a five-year survival rate of 85% among patients receiving nocturnal HHD (NHHD), a rate comparable with that of patients who had received a deceased donor transplant in the USA.[42] The Frequent Hemodialysis Network (FHN) Nocturnal Trial, randomising dialysis patients to either CHD (home or in-centre) or NHHD (six times a week), did not find a significant effect of NHHD on outcome.[43] The lack of differences in the latter trial is likely due to the small number of patients enrolled, an increased number of incident uraemic patients enrolled (> 50%) whose residual kidney function could likely have blunted the beneficial effects of the frequent dialysis, a remarkably low mortality rate in the CHD group, and the fact that one-third of the NHHD patients were less adherent to the treatment with less than 80% of the prescribed dialysis sessions done. Johansen et al. compared intensive (both nocturnal and frequent) HHD with in-centre CHD, using propensity score matching, and reported an HR of 0.36 (95% CI 0.22-0.61) for death, favouring NHHD. SDHD was not associated with a survival advantage (HR 0,64, 95% CI 0,31-1,31).[38] The FHN Daily Trial, randomising dialysis patients to in-centre SDHD (six times a week) or in-centre CHD, found a survival benefit in the SDHD treatment group.[44] A recent observational study in a large cohort of Canadian HHD patients did not find a reduction in the relative risk for the composite of death and treatment failure in patients treated with either NHHD or SDHD, after multivariable adjustment for patient and centre factors (e.g. vascular access type), compared with home CHD (NHHD: HR 0.83, 95% CI 0.66-1.03; SDHD: HR 0.84, 95% CI 0.63-1.12).[45] This could be explained by low mortality rates in all home dialysis groups. Although this study did not demonstrate a benefit of dialysis intensity, potential advantages of treatment in the home environment could not be studied due to the lack of an in-centre treatment group.

Summarising, evidence is growing for improved survival from intensive forms of haemodialysis (frequently but not invariably performed at home), as compared with conventional HD (mostly performed in-centre).

Blood pressure

Blood pressure (BP) control is one of the most consistent benefits of intensive HD in randomised and non-randomised studies.[43,46-51] One of the first reports of improved BP control in intensive HD came from France, where mean ambulatory BP was shown to be inversely correlated with HD session duration.[52] Subsequently, the FHN study showed a significant reduction in systolic BP of -9.7 mmHg (range from -16.9 to -2.5) during 12 months of follow-up in the NHHD cohort, with a significant decrease in the number of antihypertensive agents.[43] The lack of significant difference in BP readings in patients on a CHD prescription (4 hours, 3 times a week) although performed in the home setting, illustrated the importance of intensive HD as opposed to location of HD delivery as the main factor driving BP control. NHD reduces BP by lowering of total peripheral resistance and plasma norepinephrine levels.[49,50] Another factor leading to improved BP control is improved fluid balance, as achieved by SDHD.[48]

Cardiac indices

Evidence from studies with SDHD[44,48,53] and N(H)HD[46,48,54] demonstrated that intensive HD is associated with improvements in left ventricular mass index and left ventricular hypertrophy, which are factors associated with cardiovascular morbidity and mortality in dialysis patients including heart failure and sudden arrhythmic death.[55] These findings are confirmed by a recent meta-analysis of observational studies and data from RCTs that reported improvement in left ventricular mass index and geometry in both frequent and prolonged HD groups.[56] Furthermore, a cross-sectional study demonstrated that intensive HD regimens (home or in-centre) were associated with a significant reduction in intradialytic systolic hypotension and dialysis-induced myocardial stunning compared with in-centre CHD.[57] A Dutch randomised cross-over study recently confirmed improvement of haemodynamic

(peripheral systolic, peripheral diastolic and central BP) and cardiac stability, associated with better preservation of relative blood volume, during prolonged haemodialysis sessions as compared with CHD sessions.[58] Finally, two retrospective observational Canadian studies showed that frequent NHHD is associated with improvement of electrocardiographic features linked to sudden cardiac death.[59,60]

Elimination of the long (2-day) interdialytic interval over the weekend, inherent to a thrice-weekly dialysis regimen, may be an important factor in reducing cardiovascular risk with intensive HD since fluid overload and metabolic derangements (e.g. hyperkalaemia) are more pronounced after the long interdialytic interval and may lead to cardiovascular events and mortality.[61-63] Evidence from retrospective observational studies with in-centre CHD suggest that myocardial infarction, dysrhythmia, heart failure, stroke and all-cause mortality (including sudden and cardiac death) are higher on the day after the long interdialytic interval than during any other day of the week.[64-69] This pattern was not observed in patients receiving in-centre CHD > 3x/week, HHD (~70% performed dialysis thrice weekly for > 4 h per session and ~20% > 3x/week) or peritoneal dialysis.[65] However, an observational cohort study using the US Renal Data System did not find a reduced risk of arrhythmia-related hospital admissions for daily HHD patients as compared with matched in-centre CHD patients. Of note, the risk of heart failure-related admission was ~40% lower.[70] Prospective, preferably randomised, trials are required to determine whether intensive (H)HD reduces sudden cardiac death, cardiovascular morbidity and mortality in HD patients.

Bone mineral metabolism

The cumulative evidence points towards improved management of bone mineral abnormalities by the use of intensive HD.[43,56,71] It is common for patients on intensive HD prescriptions to require fewer phosphate binders, and they frequently need phosphate supplementation in the dialysate.[72] In the long term, improved control of hyperphosphataemia and secondary hyperparathyroidism by intensive HD may translate into significant risk reduction of vascular calcification, potentially contributing to increased survival in this dialysis population. Up to now, data regarding vascular calcification in HHD are inconclusive.[73]

Anaemia control

Normochromic (renal) anaemia and iron deficiency anaemia are extremely common in the dialysis population.[74] It is unknown whether intensive (H)HD has a direct effect on haemoglobin levels or erythropoietin resistance. In observational studies in HHD increased haemoglobin levels were found after intensified treatment.[75-77] Yet, an RCT did not find a difference in haemoglobin levels or erythropoietin-to-haematocrit ratio between intensive HD and CHD.[54] Evidence from observational studies suggests that erythropoiesis-stimulating agent requirement seems to decrease with intensive home treatment,[76,77] even in comparison with a propensity-score-matched in-centre CHD arm.[78] However, in the FHN nocturnal trial, erythropoietin dosage was not different between the NHHD and the CHD treatment arm.[43]

Iron supplementation is favoured in the form of intravenous iron, as a better effect on haemoglobin levels is expected.[79] However, intravenous iron administration at home is controversial, as serious adverse events (e.g. anaphylactic reactions) might occur.[80] This might be a logistic barrier to perform HHD. The Dutch Federation of Nephrology has therefore developed a practical standard for intravenous iron administration at home. Recommendations include administration of a limited amount (maximal 100 mg each time) of non-dextran iron (less known for adverse events) in no less than 30 minutes, by trained patients or nurses with uncomplicated single administration in a centre as prerequisite.[81]

Pregnancy outcomes

Another important benefit of intensive HD is its effect on fertility. Conception rates and pregnancy outcomes are overall poor in patients on dialysis. There are emerging observational data from patients on intensive HD with lower urea levels that show significantly better pregnancy outcomes compared with CHD.[82-85] It is thought that the increased rates of successful conception observed in child-bearing age female ESRD patients receiving intensive HD may be partially due to restoration of the pituitary-hypothalamic axis augmented by improved solute clearance. At the same time, improved clearance (lower urea levels), fluid balance, BP control and haemodynamic stability in intensive HD, could positively impact on pregnancy outcomes.[85,86] In the male population, intensive HD (NHHD) could also improve fertility, possibly by an increase in testosterone levels and decreasing hyperprolactinaemia.[87]

Quality of life

The impact of home intensive HD on quality of life (QoL) has been the subject of multiple studies, and overall results show an increase in kidney-specific domains of QoL parameters.[47,54,88-91] This increase in QoL with intensive HD regimes may be due to increased autonomy and functionality, reduced pill burden, liberalisation of dietary restrictions and fluid intake, considerable reduction in the time spent in the hospital and in transit to and from the hospital, optimised employment (productivity), and a reduction of inflammation and uraemic symptoms.

NHHD has been shown to be associated with mood improvement, an important domain of QoL associated with improved outcomes.[54] This might be due to improved sleep quality due to a reduction in sleep apnoea with NHHD. The FREEDOM study showed a reduction in the prevalence of restless legs syndrome from 35 to 26% after 12 months of home SDHD (p = 0.05),[92] while NHHD has been associated with a reduction in the frequency of sleep apnoea episodes.[93]

VASCULAR ACCESS

Type of access

A well-functioning vascular access is of crucial importance for safe and long-lasting HHD. According to the European Best Practice Guideline on vascular access,[94] an autogenous arteriovenous (AV) fistula is the vascular access of choice in all HD patients. As fear of self-cannulation is the most frequently reported barrier in HHD,[95] a central venous catheter (CVC) might be considered to be a suitable type of access for HHD. However, in the in-centre HD population CVC use has been associated with a higher risk of death.[96] Of course, this could be explained by differences in patient type between patients with an AV fistula vs. CVC (confounding by indication). However, equivalent results can be found in recent literature in the NHHD and HHD population: patients with CVC treated at home have a higher mortality risk compared with patients with an AV access,[97] even in a propensity-matched cohort.[98] In addition, using a CVC was associated with a higher risk for hospitalisation and local infections.[98,99] Overall, AV fistulas are the first choice and AV prosthetic grafts are preferred over CVCs.[94] CVCs should be reserved for a select group of patients with severe artery disease, severe heart failure, malignancy or anticipated short time to kidney transplantation. Also in elderly patients with limited life expectance, a CVC might be an acceptable choice.[100,101]

Self-cannulation and buttonhole vs. rope ladder technique

HHD patients performing self-cannulation obtain the highest possible independency. In the Netherlands, patients are trained in less than three weeks with the 'Tandem-hand' cannulation: the first week the nurse inserts the needle under physical guidance of the patient, the next week the patient inserts the needle with physical guidance of the nurse, the last week the patient performs the cannulation by himself in the nurse's presence.[102] The buttonhole technique, or constant site technique, was first described in 1977.[103] Due to repeated insertion of the needle at exactly the same site and in the same angle, in 2-3 weeks' time a tunnel of fibrous tissue is formed allowing successive insertion with blunt needles. In daily practice, the buttonhole technique is frequently used in patients with fear of self-cannulation since this technique is believed to be less painful. Yet in the HHD literature no significant effect on cannulation pain was found with the buttonhole technique,[104] although this study is likely biased since it included a selection of patients experiencing painful cannulation. A definitive advantage is improved survival of AV fistulas, including a reduction of aneurysm formation and reduced need of access interventions, with buttonhole instead of the rope ladder technique.[105-107] The biggest concern with buttonhole remains the risk of infections: in a systematic review more infections were found in the buttonhole group compared with rope ladder cannulation (combined RR 3.18, 95% CI 2.12-4.77).[108] In conclusion, rope ladder is the preferred method for cannulation. Yet, in patients with a short fistula and fear of self-cannulation, buttonhole remains a possible alternative if preventive hygiene is strictly followed.[109]

Surveillance

In HD in general, recommendations for access surveillance comprise access flow measurement at least every month in AV grafts and every 3 months in AV fistulas,[94,110] and there is no reason to deviate from these recommendations in HHD. Frequent monitoring reduces the risk of thrombosis formation.[111] As a routine measure, physical examination prior to any cannulation is recommended in order to identify possible access problems. Patients should be taught how to recognise infections, aneurysm and stenosis and they might benefit from retraining programs.[22,112] The 'Arm Raise Technique' is an easy tool used to detect a possible stenosis.[113] The biggest challenge in HHD is to incorporate frequent monitoring in the home environment. In some HHD centres, patients are invited to perform in-centre HD once every 2-3 months, in order to perform the access flow measurements. In the Netherlands, access flow measurements are executed at home (personal communication).

Access failure and infections

As previously described, HHD presents many advantages above in-centre CHD, but has possible additional complications.

In the FHN trials, *the time to first access event* (the composite of vascular access associated hospitalisation, repair and loss) was shorter with SDHD and NHHD compared with CHD (HR 1.76, 95% CI 1.11-2.79 and HR 1.81, 95% CI 0.94-3.48, respectively).[114] Of note, buttonhole was associated with a longer complication-free period in comparison to the rope ladder technique. In the separate (underpowered) FHN studies, vascular access events were seen more frequently during follow-up, yet this was not significant (Daily trial HR 1.35, 95% CI 0.84-2.18 (n = 245)[44]; Nocturnal trial HR 1.62, 95% CI 0.91-2.87 (n = 87)[43]). Most importantly, the access

failure rate (single outcome) in NHHD and SDHD was comparable with in-centre CHD.[43,114] We suggest that double needling might be associated with higher repair risks in these trials on frequent dialysis, yet no studies are available comparing complications in single-access needling (often performed in frequent NHHD in the Netherlands) and double-access needling. A well-founded advice on single versus double needling can therefore not be given. As expected, access failure is dependent on vascular access type: an access failure rate of 0.02-0.16/ patient-years was reported in patients using an AV fistula or graft, whereas the rate in patients with a CVC was higher: 0.48-1.07/ patient-years.[99,114-120]

The event rate of thrombolysis in HHD ranged from 0.27-1.60/ patient-years in patients using CVC. In patients using an AV fistula no thrombosis was seen during a follow-up of 6 months.[121] Due to less exposure to pathogens in hospitals, patients on HHD are believed to be less susceptible to infections. Yet, patients treated with intensive HHD (5-6 sessions weekly) were hospitalised for infection more frequently than in-centre CHD patients.[70] Possible explanations for this finding include frequent use of the buttonhole technique, mediocre preventive hygiene, and an association with frequent dialysis. Patients performing NHHD and using the buttonhole technique were three times more likely to develop a vascular access-related sepsis than patients performing CHD.[116]

OTHER COMPLICATIONS

There is a lack of data comparing HHD events to in-centre dialysis events. Tennankore et al. report the occurrence of technical adverse events and severe events requiring intervention at a rate of 0.16 and 0.038 per 1000 dialysis sessions in a cohort of HHD patients dialysing a median of 5 times a week and 8 hours a session.[122] The study by Wong et al. described a life-threatening event rate of only 0.060 per 1000 dialysis sessions.[123] Thus, current literature indicates that the overall event rates for these complications are acceptably low, which confirms the safety of HHD, but the potential for life-threatening events warrants discussion.[49,124] These specific complications relate to three main areas: 1) dialysis techniques; 2) medical factors; and 3) psychosocial aspects.[125]

Examples of errors in dialysis techniques include machine dysfunction, misuse of dialysis line set, inadequate preparation or contamination of water, and dialysis composition. To prevent technical complications, an adequate education and retraining program for the patient and/or dialysis partner is essential, in addition to accurate protocols and a staff member available 24 hours a day. It is also important to maintain patient awareness of the necessity of these safety protocols.

Successful HHD requires reliable vascular access. Most of the described medical events arose due to AV fistula or graft cannulation needle dislodgements, which were clearly related to patient error or equipment malfunction.[122] An unobserved major bleed due to needle dislodgement during nocturnal dialysis is an important possible medical complication. Nevertheless, this risk can be reduced by securing the needles or the CVC with adhesive plasters and by using detector alarms to indicate blood loss. However, in the study by Tennankore, half the patients were not using the offered detector at the time of the event. In the case of nocturnal dialysis, it is possible to reduce this risk by using one needle, with still superior dialysis efficiency compared with a conventional regimen. A few reports address air embolism in the home setting, the majority of which were related to patient error.[122,123]

Other possible medical complications of HD, including HHD, are hypotensive collapse or cardiovascular instability. However, intensive HHD is also known to be more effective for attaining cardiovascular balance. The safety of NHHD is enhanced by decreasing the ultrafiltration, blood flow and dialysate flow rates. Finally, the medical team should be alert to nutritional deficiencies, especially with regard to phosphate and the water-soluble vitamins. Despite the fact that these vitamins are supplemented after each HD session, we have identified substantial vitamin C deficiency in a significant number of our patients, especially those on intensive HD. Phosphate can be added to the dialysate in the form of phosphate enemas.[72]

Psychosocial complications are often underestimated, but they influence the endurance of the HHD patient and/ or partner.[125] Long-term treatment could lead to anxiety, depression and fatigue because of the perceived 'gloomy future' and the demands placed on the patient in terms of time and effort. This may lead to non-compliance and treatment failure. Therefore, psychosocial support is needed before and during the treatment period and the medical team should remain focused on these possible problems.

Thus, several reasons can explain treatment failure in HHD. Recent cohort studies determined that 18-25% of patients discontinued HHD treatment within the first year. Human error is the most common factor contributing to complications arising in the home setting, and usually results from not adhering to prescribed protocols. A high quality and successful HHD program must focus on minimising possible complications, improving event reporting and providing retraining. Therefore, it is important that a dialysis centre offering this modality is experienced in HHD and that patients and staff are trained to detect complications at an early stage. Emergency care for major events should be optimised and in-centre dialysis should be available to patients who fail in HHD. If these

factors are considered, the risks for complications are minimal.

BARRIERS TO HOME HAEMODIALYSIS

Despite the benefits of HHD compared with in-centre HD, the majority of dialysis patients (82%) in the Netherlands are treated in-centre with CHD. Both physician- and patient-perceived barriers prevent patients from adopting HHD.

Physician attitudes towards HHD are positive. Surveys among nephrologists indicate that there is a strong belief in the benefits of intensive HD and that home is considered the best location for dialysis.[126-130] The estimated percentage of patients considered medically and psychosocially fit to perform home dialysis ranges from 15 to 25%,[13,18] which exceeds the current proportion of HHD patients in most countries by far. Physician-perceived barriers may, at least in part, explain the discrepancy between physicians' beliefs in HHD and current practice patterns. The perceived lack of patient motivation is one of the most frequently cited reasons not to start HHD,[126,131,132] and may be related to suboptimal pre-dialysis patient education programs. Other commonly reported barriers are related to patient characteristics (e.g. age, comorbidities, cognitive impairment, socioeconomic disadvantages), complexity of the dialysis procedure, limited infrastructure (e.g. lack of training facilities), lack of dedicated resources (e.g. multidisciplinary team to educate and support HHD patients), and lack of expertise by nephrologists.[126,133] The increased number of vascular access events in nocturnal HHD patients who perform self-cannulation may also play a role.[43] Other concerns are related to the costs of HHD. In the Netherlands, health insurers offer standard reimbursement rates for in-centre HD and HHD. This system is a disincentive to dialysis centres supporting patients on more intensive dialysis schedules and providing assistance by a home dialysis nurse, which are accompanied by higher actual costs compared with self-supported home CHD. This could be counteracted by accurate knowledge of the actual costs followed by offering more differentiated reimbursement rates by healthcare providers, more closely related to the actual costs of dialysis care. The DOMESTICO (Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes) study group aims to conduct a large cohort study including home dialysis patients, to map actual costs of home dialysis, study examples of good practice and overcome barriers.

From a patient perspective, reasons not to opt for HHD are related to fears and the burden of undertaking HHD. The major barriers perceived by in-centre HD patients are lack of explanation of self-care dialysis, fear of self-cannulation, fear of a catastrophic event in the absence of medical staff support, the burden placed on family caregivers, lack of self-confidence and/or self-efficacy in performing dialysis at home and a coinciding fear of receiving substandard care.[134-137] Other reported barriers are a belief that patients should be supervised by medical staff, fear of social isolation, interference of treatment with home life, reluctance to perform the required home adaptations and insufficient space to store equipment and supplies.[136,137] Physician and patient perceived barriers have to be overcome to expand HHD practice. Motivation and education of both patients and staff is essential to achieve this.[138,139] Specialised training in HHD for nephrologists will create awareness of the benefits of this modality and encourage them to offer this treatment to patients. The characteristics and effectivity of a CPE program were addressed in the paragraph 'Patient education'. When patients opt for HHD, a patient-tailored plan should be drawn up. Allowing and encouraging patients to perform HHD independently of a family caregiver may enable more patients to adopt HHD and decrease the perceived burden on family members. Experiences from the UK and Finland show that solo-dialysis is feasible for the vast majority of HHD patients.[140] The support of a skilled home dialysis nurse may facilitate HHD in the absence of a family caregiver, in the case of debilitated patients or the elderly, who are now often considered poor candidates for HHD, and for patients with a CVC.[141,142] Staff-assisted HHD eliminates the need for patient training and can be initiated immediately after installation of the equipment at home. It increases the patient's confidence in HHD and motivates patients to take responsibility and start a training program for self-supported HHD. The experience of a Dutch dialysis unit with 10 years of staff-assisted HHD shows that 30% of the patients starting with staff-assisted HHD can be converted to solo-dialysis or family-supported HHD (personal communication). Also, a hybrid of staff-assisted HHD and self-assisted HHD can be applied. For instance, when a patient and partner are afraid of self-puncturing, but can be responsible for the dialysis procedure, a skilled dialysis nurse can simply do the puncturing for them. Last, the design of less complex HHD devices requiring less storage space and less home modifications and the application of remote monitoring technology[143,144] may improve patients' confidence to perform dialysis independently and effectively without direct supervision of medical staff, and in addition may shorten time of HHD training programs and lower the costs.

NEW DEVELOPMENTS

The increased popularity of HHD has stimulated the development of less complex, transportable (24-34 kg) and more user-friendly dialysis machines (see dialysis machines).[145,146] All of these machines are low-dialysate-

flow systems (max 300 ml/min) requiring an increased time on therapy (typical treatment scheme: 4-6 times per week 2.5-4 hours). In the near future the release of a new compact (45 x 37 x 48 cm) cartridge-based dialysis machine of 29 kg suitable for HHD is expected (not yet FDA approved or CE certified).[147] The device needs a domestic water treatment system, but dialysate flow rates up to 500 ml/min can be applied.

The weight of the transportable HD machines is still considerable (≥ 24 kg) and all systems rely on conventional technology using pre-mixed or in-situ mixed dialysate (≥ 20 litres per treatment) in a single pass configuration. Continuous regeneration and reuse of a small amount of dialysis fluid in a closed-loop system renders the system independent of a large dialysate supply and allows further miniaturisation, but the technology is challenging. Currently, a portable artificial kidney of ~10 kg using ~6 litres of dialysate, is being developed by a collaborative effort of the Dutch Kidney Foundation and several biotechnology companies, based on the REDY (REcirculation DialYsis) technology combining adsorbent, ion exchange and enzyme techniques.[148] The device will be designed for every-other-day HHD. A functional model became available in 2016 and a first in-human clinical trial is expected to start in 2019. Other companies are working on comparable sorbent HD systems.[149,150] In the meantime, initiatives towards further reducing the dimensions to wearable proportions, allowing maximum flexibility for the patient, are ongoing. One of the major challenges is urea removal since direct adsorption of urea is very difficult while a relatively large amount needs to be removed daily (around 400 mmol ≈25 grams).[151] A wearable artificial kidney of 5 kg relying on urease (as the REDY technology) has been designed. Urease is an enzyme that catalyses hydrolysis of urea to carbon dioxide/bicarbonate and ammonia/ammonium. The device was successfully tested in a first-in-human trial during 24 hours (FDA fast track status).[152] However, removal of ammonium, which is more toxic than urea, requires extra sorbent (zirconium phosphate) and solutes (i.e. concentrated infusate with cations removed by zirconium phosphate and sodium bicarbonate to neutralise protons released in exchange for ammonium) which limits further miniaturisation. Initiatives to develop alternative urea removal strategies allowing further miniaturisation to truly wearable proportions (< 1.5 kg) such as direct adsorption[153] and electrochemical urea degradation[154] are ongoing but still far from clinical application.

Another development in the field of HHD is the application of remote telemonitoring systems to record patient- and treatment-related parameters and allow for (face-to-face) communication.[155,156] This could reduce patients' experiences of social isolation and anxiety about the absence of medical staff, reduce travel time and enable health professionals to monitor treatment and compliance more continuously, advise patients on how to adjust their treatment themselves, and facilitate remote assistance in case of acute problems.

The Dutch Kidney Foundation is supporting some of these new developments, and also stimulates the different forms of home dialysis by the recent initiation of a Taskforce Home Dialysis.

CONCLUSION

It is difficult to make practice recommendations regarding HHD based on the current body of evidence. There is a lack of large RCTs, which are not feasible to perform. Well-matched prospective cohort studies on a broader range of outcomes (e.g. quality of life, hospitalisations, vascular access associated complications, blood pressure control) are needed to provide greater certainty about the clinical benefits of HHD. However, current evidence indicates that intensive HD, facilitated in the home setting, is associated with improved clinical outcomes at the expense of more vascular access complications. Although severe and life-threatening events rarely occur in HHD, strict regulations combined with patient education and retraining on technical issues, preventive hygiene and emergency situations are important. In order to provide a high level of care, in both knowledge and logistics, a dedicated and experienced team is needed. National initiatives to promote learning between centralised dialysis facilities and regional centres are currently in development in the Netherlands.

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ORIGINAL ARTICLE

Classifying sepsis patients in the emergency department using SIRS, qSOFA or MEWS

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ABSTRACT

Objective: To determine the effect of qSOFA and SOFA compared with the MEWS and SIRS criteria on the classification of emergency department (ED) patients with an infection as having sepsis.

Methods: A retrospective single-centre study was performed in a random sample of 600 medical patients who visited the ED of the Academic Medical Centre Amsterdam between 1 November 2015 and 1 November 2016. Data for the different sepsis scores, as well as general data and demographics were retrieved. Descriptive analytics and sensitivity/specificity analysis were used to evaluate the performance of the different sepsis tools.

Results: Of 577 evaluable medical patients, 198 patients (34.3%) had a probable infection. The SIRS sepsis criteria, severe sepsis criteria, MEWS ≥ 5 and qSOFA criteria classified 141/198 (71.2%), 55/198 (27.8%), 58/198 (29.3%) and 17/198 patients (8.6%) respectively, as septic. The in-hospital mortality of patients classified as septic by the SIRS and qSOFA score was 6.4% and 29.4%. The qSOFA and SIRS score of ≥ 2 had a specificity of 93.7% (95% CI: 91.3-95.6) and 56.9% (52.7-61.1) in predicting in-hospital mortality.

Conclusion: No major differences in gender, age, comorbidity and site of infection between patients with sepsis or severe sepsis classified by the SIRS, qSOFA criteria or MEWS of ≥ 5 were found. The qSOFA criteria classifies a smaller group of patients as septic compared with the SIRS or MEWS. Due to this strict selection, the qSOFA score seems unsuitable as a bedside tool in the work-up and treatment of sepsis at the ED.

KEYWORDS

MEWS, sepsis, SIRS, qSOFA

INTRODUCTION

Sepsis is a serious medical condition where infection leads to systemic inflammation and finally organ dysfunction. Based on incidence rates in seven high-income countries, the estimated global incidence of hospital-treated sepsis and severe sepsis is 437 and 270, respectively, per 100,000 inhabitants.[1,2] The incidence of sepsis and severe sepsis has increased in the last few decades, probably due to better recognition and increasing age.[3] The incidence of sepsis is age-related with an increased incidence in both infants (< 1 year) and the elderly (> 65 years).[4,5] Mortality and long-term morbidity, especially among elderly patients with sepsis, is high.[6]

Since 1991, the Systemic Inflammatory Response Syndrome (SIRS) criteria have been used to classify sepsis (*table 1*).[7] At an International Sepsis Definitions Conference in 2001 it was concluded that the SIRS criteria were too non-specific to diagnose systemic inflammation caused by an infection. However, due to the high sensitivity in predicting systemic inflammation, the SIRS criteria were maintained.[8] As a result of growing criticism on the low specificity of the SIRS criteria, an update of the sepsis definition and criteria was needed.[9] Early 2016, an international sepsis task force published a new international consensus for the definition of sepsis. They defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[10] The new sepsis definition uses a set of clinical and biochemical criteria called the Sequential Organ Failure Assessment (SOFA) (*table 2*). The SOFA score is mainly based on biochemical criteria and therefore the task force developed the more clinical qSOFA screening tool which is based on respiratory rate, systolic blood pressure and an altered mental state (*table 1*). The new sepsis definition requires a change in the SOFA score of two or more points following an infection. According to the task force, the new sepsis

Table 1. *SIRS criteria and qSOFA score*

SIRS criteria (≥ 2)	Body temperature > 38.0 °C or < 36.0 °C
	Heart rate of > 90/min
	Respiratory rate of > 20 breaths/min or $PaCO_2$ of < 4.3 kPa
	White blood cell count of < 4000 cells/mm³ or > 12,000 cells/mm³ or > 10% immature bands
qSOFA score (≥ 2)	Respiratory rate ≥ 22 breaths/min
	Systolic blood pressure ≤ 100 mmHg
	Altered mental state

SIRS = systemic inflammatory response syndrome; qSOFA = quick sequential organ failure assessment.

Table 2. *Sequential Organ Failure Assessment (SOFA) score*[10]

Organ system		Score				
		0	1	2	3	4
Respiratory	*PaO_2/FiO_2 (kPa)*	≥ 53.3	< 53.3	< 40	< 26.7	< 13.3
Renal	*Creatinine (µmol/l)*	< 110	110-170	171-299	300-440	> 440
Hepatic	*Bilirubin (µmol/l)*	< 20	20-32	33-101	102-204	> 204
Haematological	*Platelets x10³/µl*	≥ 150	< 150	< 100	< 50	< 20
Neurological	*Glasgow Coma Score*	15	13-14	10-12	6-9	< 6
Cardiovascular		MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine	Dopamine 5.1-15, epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[A]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[A]

[A]Adrenergic agents (µg/kg/min) given for at least 1 hour.
MAP = mean arterial pressure.

definition is more focussed on the severity of organ dysfunction in patients with an acute infection than the traditional SIRS score. As such, it is supposed to have a higher specificity in identifying patients with more severe and life-threatening infections.

Early recognition and treatment of sepsis is important to reduce mortality, hospital length of stay and morbidity.[11,12] While the qSOFA score is not part of the new sepsis definition, it is an important part of the sepsis work-up in the ED.[13,14]

Although the performance of qSOFA in relation to ICU hospitalisation and mortality has been studied in large prospective datasets, the interrelationship between various scores, i.e. the similarities and differences between the patient groups classified as septic by these scores, is unclear.[15]

The new definition can enhance research in the treatment of more critically ill sepsis patients. However, until now all research on early antibiotic treatment of sepsis has been based on the SIRS criteria. Thus it is not known what the consequences of the changed sepsis definition are for early antibiotic treatment in patients who are no longer classified as septic according to the new guideline.

This study aims to determine the effect of qSOFA and SOFA compared with the MEWS (*table 3*) and SIRS criteria on the classification of patients with an infection as having sepsis and its performance compared with the MEWS and SIRS criteria.

METHODS

Study design and setting

A retrospective single-centre study was performed to evaluate the difference in the number of medical patients in the ED classified as septic by either the SIRS, SOFA criteria or MEWS and their mortality. Medical records of 600 medical patients (18.4% of all medical patients) who visited the ED of the Academic Medical Centre Amsterdam (AMC) between 1 November 2015 and 1 November 2016 were randomly included. The AMC is a 500-bed tertiary care hospital linked to the University of Amsterdam (UVA) in the southeast of Amsterdam, the Netherlands.

This study was approved by the review board for reuse of care data of the AMC. Due to the retrospective

Table 3. *Modified Early Warning Score (MEWS)*[15]

Score	3	2	1	0	1	2	3
Respiratory rate (breath/min)		< 9		9-14	15-20	21-29	≥ 30
Heart rate (bpm)		≤ 40	41-50	51-100	101-110	111-129	≥ 130
Systolic blood pressure (mmHg)	≤ 70	71-80	81-100	101-199		≥ 200	
Temperature (°C)		< 35,0		35-38.4		≥ 38.5	
AVPU				Alert	reacting to Voice	reacting to Pain	Unresponsive

observational nature of the study, no formal approval from the Medical Ethics Committee was necessary.

Selection of participants

Patients had to meet the following criteria to be included: (1) patients were ≥ 18 years old; (2) patients visited the ED and were seen by the internal medicine department or its subspecialties, rheumatology, gastroenterology, pulmonary and respiratory diseases, vascular diseases, intensive unit or the department of geriatric medicine. Patients were included only once regardless of the number of consultations at the ED. However, the number of repeat visits was recorded. If patients consulted the ED more than once with a probable infection, the first consultation was selected. Only when a patient was hospitalised at a subsequent consultation at the ED was the consultation that led to hospitalisation selected. After randomisation and screening of the medical records, patients were only excluded from analysis if none of the vital signs (temperature, blood pressure and heart rate) were noted during the ED consultation.

Methods and measurements

All data necessary for the SIRS (temperature, heart rate, blood pressure, respiratory rate, $PaCO_2$, leukocytes), qSOFA, SOFA (Glasgow coma scale, altered mentation, blood pressure, respiratory rate, PaO_2/FIO_2, serum thrombocytes, bilirubin, lactate and creatinine and the use of vasopressor agents) and MEWS, as well as general demographics such as age, gender and comorbidities were retrieved from the medical records. Also, data about laboratory tests, cultures, radiology examination and interventions performed on the ED and within the first 48 hours of admission to the hospital were collected.

Probable infection was based on the final diagnosis in the discharge letter after hospitalisation or the ED visit and confirmed by an independent review of the medical record by the principal investigator, who was not involved in patient care during this period. Where discrepancies seemed to exist between the discharge letter and the review by the principal investigator due to new insights, e.g. cultures turning positive after discharge, the case was subjected to further review by a second senior investigator. Proven infection was defined as a positive blood, urine, sputum, wound or ascites culture that was considered to be clinically relevant by the attending physician from the medical department.

SIRS, qSOFA, SOFA and MEWS scores were calculated from the collected data to classify patients with sepsis and severe sepsis. Sepsis based on the SIRS criteria was defined as a probable infection combined with a SIRS score of ≥ 2 points. Severe sepsis was defined as a probable infection, a SIRS score of ≥ 2 points and organ dysfunction (SOFA score ≥ 2). Since mortality risk increases strongly at MEWS ≥ 5, sepsis according to MEWS was based on a MEWS ≥ 5 + infection.[16]

For all calculated scores, the first noted laboratory results, temperature, heart rate, respiratory rate, lowest Glasgow Coma Score (GCS) and the lowest noted blood pressure on the ED were used. The GSC was based on the free text of the ED consultation if it was not explicitly noted. Other missing values were considered to be within the normal range.

Vital signs were measured by experienced nurses using automated blood pressure cuffs and a tympanic thermometer. FiO_2 was determined based on conversion tables for the amount and route of oxygen administered. PaO_2 was based on arterial blood gas when available, but was often missing. If no arterial blood gas was taken, no points on the SOFA score could be awarded for this parameter.

Group characteristics according to various sepsis definitions

The patient groups classified as having sepsis according to the various definitions (see *table 4*) were analysed for their characteristics, including outcome parameters such as hospitalisation and mortality.

Statistical analysis

Statistical and descriptive analytics were performed using the Statistical Package for Social Sciences (SPSS-PC version 23.0.0.3; IBM corporation). Continuous data are expressed as mean ± standard deviation (SD) and categorical data as number (%). Sensitivity and

Table 4. *Characteristics of sepsis classified by SIRS, SOFA criteria and MEWS ≥ 5*

		SIRS ≥ 2 & probable infection	SIRS ≥ 2, SOFA ≥ 2 & probable infection	MEWS ≥ 5 & probable infection	qSOFA, SOFA ≥ 2 & probable infection
		n = 141	n = 55	n = 58	n = 17
Gender	*Female*	73 (51.8)	26 (47.3)	31 (53.4)	12 (70.6)
	Male	68 (48.2)	29 (52.7)	27 (46.6)	5 (29.4)
Age, years		58.2 ± 17.9	63.2 ± 15.7	56.4 ± 20.2	63.2 ± 14.1
Comorbidity	*Immunocompromised*	34 (24.1)	11 (20.0)	13 (22.4)	2 (11.8)
	Malignancy	45 (31.9)	16 (29.1)	14 (24.1)	4 (23.5)
	Renal	26 (18.4)	13 (23.6)	13 (22.4)	3 (17.6)
	Cardiac	42 (29.8)	17 (30.9)	19 (32.8)	5 (29.4)
	Lung	50 (35.5)	22 (40.0)	17 (29.3)	5 (29.4)
	Diabetes	26 (18.4)	13 (23.6)	9 (15.5)	3 (17.6)
	No comorbidity	28 (19.9)	9 (16.4)	14 (24.1)	2 (11.8)
Hospitalisation	*All*	111 (78.7)	52 (94.5)	52 (89.7)	17 (100)
	AMC	95 (67.4)	46 (83.6)	44 (75.9)	16 (94.1)
	Other hospitals	16 (11.3)	6 (10.9)	8 (13.8)	1 (5.9)
ICU admissions		13 (9.2)	10 (18.2)	9 (15.5)	5 (29.4)
In-hospital mortality		9 (6.4)	7 (12.7)	5 (8.6)	5 (29.4)
30-day mortality		11 (7.8)	8 (14.5)	6 (10.3)	6 (35.3)
Site of infection	*Respiratory tract*	80 (56.7)	35 (63.6)	29 (50.0)	11 (64.7)
	Intestine	5 (3.5)	3 (5.5)	2 (3.4)	1 (5.9)
	Urinary tract	17 (12.1)	7 (12.7)	9 (15.5)	1 (5.9)
	Biliary tract	10 (7.1)	4 (7.3)	5 (8.6)	2 (11.8)
	Skin/ soft tissue	6 (4.3)	0	2 (3.4)	0
	Fever of unknown origin	6 (4.3)	1 (1.8)	3 (5.2)	0
	Multiple	4 (2.8)	2 (3.6)	2 (3.4)	2 (11.8)
	Other	13 (9.2)	3 (5.5)	6 (10.3)	0

Data expressed as mean ± standard deviation or number (% in group).
SIRS = Systemic inflammatory response syndrome; SOFA = Sequential Organ Failure Assessment; MEWS = Modified Early Warning Score; AMC = Academic Medical Centre Amsterdam.

specificity were calculated to evaluate the accuracy of the clinical sepsis tools (SIRS, qSOFA and MEWS ≥ 5) in in-hospital mortality. Sensitivity and specificity are expressed as percentage with 95% exact Clopper-Pearson confidence intervals.

RESULTS

Characteristics of study subjects

Between 1 November 2015 and 1 November 2016 there were 29,615 patient visits to the ED of the AMC, of which 3254 patients visited the ED for a medical problem (for a total of 4632 ED visits). Seven patients were excluded from this study because they were less than 18 years old, therefore 3247 were included for randomisation. Out of the randomly selected 600 screened medical records, 577 records were included for analysis. In eight of the excluded records there were no vital signs noted for the ED consultation and additionally 15 excluded patients presented to one of the medical specialties but were not actually seen by a doctor of one of the medical departments. The patient characteristics of the 577 medical patients are summarised in *table* 5.

Table 5. *Baseline characteristics of the included medical patients (n = 577)*

		(%)
Gender	Female	287 (49.7)
	Male	290 (50.3)
Age, years		55.3 ± 18.6
Age categories, years	18-30	71 (12.3)
	30-40	65 (11.3)
	40-50	82 (14.2)
	50-60	98 (17.0)
	60-70	125 (21.7)
	70-80	90 (15.6)
	> 80	46 (8.0)
Patients from the service area AMC[A]		298 (51.6)
Patients under current treatment outpatient clinic AMC	Total	319 (55.3)
	General medicine	20 (3.5)
	Infectious diseases	13 (2.3)
	Haematology	65 (11.3)
	Oncology	50 (8.7)
	Nephrology	50 (8.7)
	Vascular diseases	12 (2.1)
	Endocrinology	14 (2.4)
	Rheumatology	8 (1.4)
	Pulmonary and respiratory diseases	57 (9.9)
	Gastroenterology	58 (10.1)
Hospitalisation	All	312 (54.1)
	AMC	277 (48.0)
	Other hospitals	35 (6.1)
	Intensive care unit AMC	37 (6.4)
Hospital mortality		21 (3.6)
Culture within the first 48 hours and started antibiotics on the ED		175 (30.3)
Probable infection		198 (34.3)
Proven infection[B]		77 (13.3)
SIRS ≥ 2 points		253 (43.8)
SIRS ≥ 2 points + probable infection		141 (24.4)
Severe sepsis		55 (9.5)
MEWS > 5 points		77 (13.3)
MEWS > 5 points + probable infection		58 (10.1)
qSOFA ≥ 2 points		42 (7.3)
qSOFA ≥ 2 points + probable infection		31 (5.4)
SOFA score ≥ 2 points + probable infection		71 (12.3)
qSOFA ≥ 2 & SOFA ≥ 2 points		26 (4.5)
qSOFA ≥ 2 & SOFA ≥ 2 points + probable infection		17 (2.9)

Data expressed as mean ± standard deviation (SD) or number (% of all patients); [A]Area in and around the southeast of Amsterdam based on ZIP code. The AMC is appointed as regional hospital for the primary care of its inhabitants.
[B]Proven infection defined as a positive blood, urine, stool, sputum, wound or ascites culture.
AMC = Academic Medical Centre Amsterdam; SIRS = Systemic inflammatory response syndrome; MEWS = Modified Early Warning Score; qSOFA = (quick) Sequential Organ Failure Assessment.

Establishing infection and score measurements

Based on the final diagnosis in their discharge letter 198/577 patients (34.3%) had a probable infection. In 175/577 patients (30.3%), antibiotics were started on the ED and a culture was performed within the first 48 hours of admission (*table 5*).

The attending physician concluded in the discharge letter that there was no probable infection in 18 of these 175 patients. However, an additional, 41/577 patients had an infection even though antibiotics were not started and no culture was performed within the first 48 hours of admission. Of these 41 patients, 14 patients were treated for pneumonia only based on chest X-ray or clinical signs, 5 patients had malaria, 9 patients had a proven viral infection, 4 patients had a urinary tract infection, 7 patients had another kind of bacterial infection and 2 patients with a metastatic malignancy did not agree to receiving antibiotic treatment. So, in total 198 patients had a probable infection.

Eventually, 77 of these 198 patients had a proven infection defined as a positive blood, urine, stool, sputum, wound or ascites culture.

When calculating the scores, blood pressure, temperature and heart rate were available for almost all patients. Likewise, creatinine and leucocyte count were available in over 93% of cases.

On the other extreme, arterial blood gas analysis was frequently missing and in 129 patients with a probable infection no PaO_2/FiO_2 was available. In 2 patients with a probable infection no blood pressure was noted and 32 patients had no noted respiratory rate. In all patients with a probable infection a GSC was scored.

The distribution of scores in the population studied is shown in *table 5*.

Main results

The SIRS criteria classified 141/198 patients as septic (71.2%) of which 55/198 patients (27.8%) also met the criteria for severe sepsis. The combined qSOFA and SOFA score for sepsis classified 17/198 patients (8.6%) as septic and a MEWS ≥ 5 classified 58/198 patients (29.3%) as septic.

Even though the number of patients with sepsis according to MEWS ≥ 5 and according to SIRS was approximately the same (58 vs 55 patients, respectively), the scores classified different patients. Of the patients with a probable infection, 24/198 (12.1%) had both severe sepsis and a MEWS of ≥ 5 points. Almost all patients with sepsis based on the SOFA definition (88%) also had a MEWS of ≥ 5 points and severe sepsis according to the SIRS criteria. The overlap between the various definitions is shown in *figure 1*.

Patients with sepsis classified by the different clinical tools had a mean age varying from 56.4 years ± 20.2 to 63.2 ± 15.7 (*table 4*). The respiratory tract was the most common site of infection (range 50% to 64.7%) followed by the urinary tract (range 5.9% to 15.5%). All patients with sepsis classified by SOFA criteria were hospitalised compared with 94.5% of the patients with severe sepsis, 89.7% of the patients with a MEWS of ≥ 5 and 78.7% of the patients with sepsis classified by the SIRS criteria.

Twelve patients with a probable infection (6.1%) died during hospitalisation. Five out of 17 patients (29.4%) with sepsis according to the qSOFA score died during hospitalisation. The in-hospital mortality in patients with sepsis (SIRS criteria), severe sepsis and MEWS ≥ 5 was 6.4%, 12.7% and 8.6%. The overlap in in-hospital mortality between the sepsis scores is shown in *figure 1*.

Sensitivity and specificity analysis

The specificity of the different sepsis tools for predicting in-hospital mortality was 56.9% (95% CI: 52.7-61.1) for SIRS ≥ 2, 96.4% (94.5;97.8) for qSOFA ≥ 2, 87.0% (95% CI: 83.9-89.7) for MEWS ≥ 5 and 87.4% (84.3-90.0) for SIRS ≥ 2 and SOFA ≥ 2 (*table 6*). Sensitivity was poor for qSOFA [33.3% (14.6-57.0)] compared with SIRS [61.9% (38.4-81.9)]

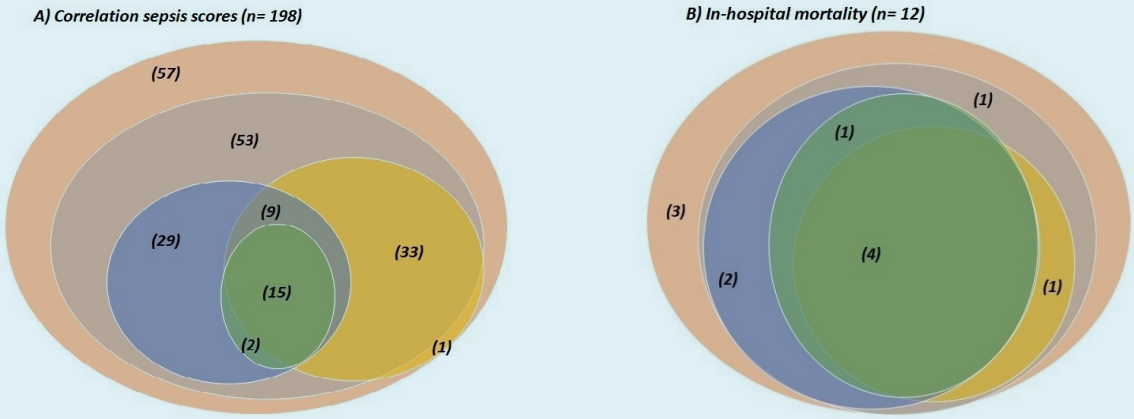
DISCUSSION

Because of their high prevalence and mortality, infectious diseases and sepsis need to be quickly identified in the ED so that early interventions may improve outcome. As shown in *table 5*, one in three of our medical patients presented with a probable infection at the ED based on the final diagnosis in the discharge letter.

The new sepsis work-up based on the qSOFA and SOFA score classified only a small group of these patients as septic compared with the traditional SIRS criteria. In fact, 88% of the patients previously labelled as septic would no longer be considered septic due to the change in sepsis definition. However, as designed, the combination of qSOFA + SOFA ≥ 2 did succeed in classifying a small group of patients with life-threatening organ dysfunction and increased mortality (*table 6*). Patients with sepsis classified by these criteria had an in-hospital mortality of 29.4%.

Although the qSOFA score is not part of the sepsis-3 definition, it plays an important role in the sepsis work-up in the ED. Effectively, the qSOFA is meant to replace the SIRS score as a bedside tool to recognise sepsis in the ED. Only 15.7% of those with a probable infection scored ≥ 2 points on the qSOFA score, while 35.9% patients with a probable infection scored ≥ 2 points on the SOFA score (*table 5*). Thus, the qSOFA score failed to classify 40/71 patients (56.3%) as septic who would have been considered septic if only the SOFA score were used. This is in line with the study by Freund et al. who reported that 25% of ED patients with a probable infection have a qSOFA

Figure 1. *Correlation between probable infection, MEWS, sepsis and severe sepsis and in-hospital mortality. A) Number of patients with a probable infection, sepsis and severe sepsis classified by the SIRS and SOFA criteria and MEWS ≥ 5. B) Overlap in in-hospital mortality between the sepsis scores (out of total 198 patients with a probable infection)*



Legend:
- Probable infection
- SIRS ≥ 2 & probable infection
- SIRS ≥ 2 + SOFA ≥ 2 & probable infection
- MEWS ≥ 5 & probable infection
- qSOFA ≥ 2 + SOFA ≥ 2 & probable infection

score of ≥ 2 while 34% of the patients have a SOFA score of more than two points.

The strict selection by the qSOFA score is mainly accounted for by the small number of patients with a probable infection who had an altered mental state (20 patients (10.1%)). Of all patients with a probable infection, 52 patients (26.3%) had a systolic blood pressure of ≤ 100 mmHg and 66 patients (33.3%) had a respiratory rate of ≥ 22/min. Recent studies by Churpek et al., Freund et al. and Williams et al. similarly found a positive qSOFA score (≥ 2) in only 9%, 25% and 10.2% of their patients at the time of suspicion of infection.[15,17,18]

MEWS is normally used for early recognition of clinical deterioration of hospitalised patients and was not originally designed for recognition of sepsis patients. However, MEWS ≥ 5 selected approximately the same number of patients as severe sepsis when compared with the SIRS criteria. Although these scores select different patients within the sepsis spectrum, there were no major differences in ICU admissions or site of infection (*table 4*). The overlap in patients classified by the various scores is shown in *figure 1*.

Due to the high prevalence of positive SIRS criteria in patients in the ICU, the SIRS score is not very useful as a clinical tool in the recognition of sepsis in ICU patients. Therefore, a score with a higher specificity in predicting infection and mortality like the qSOFA score in the ICU is needed. Despite this, recent studies report that the predictive value of the qSOFA score for in-hospital mortality is better outside the ICU compared with patients admitted to the ICU.[18-20] In the ED on the other hand, a clinical tool with a high sensitivity in predicting organ dysfunction and mortality is more important, to avoid

Table 6. *Sensitivity and specificity for in-hospital mortality (n = 577)*

	In-hospital mortality (n = 21)	
	Sensitivity	*Specificity*
SIRS ≥ 2	61.9% (38.4-81.9)	56.9% (52.7-61.1)
qSOFA ≥ 2	33.3% (14.6-57.0)	93.7% (91.3-95.6)
SOFA ≥ 2	66.7% (43.0-85.4)	79.8% (76.2;83.1)
qSOFA ≥ 2 + SOFA ≥ 2	28.6% (11.3-52.2)	96.4% (94.5;97.8)
MEWS ≥ 5	23.8% (8.2-47.2)	87.0% (83.9-89.7)
SIRS ≥ 2 + SOFA ≥ 2	42.9% (21.8-66.0)	87.4% (84.3-90.0)

Sensitivity and specificity expressed as percentage with (95% exact Clopper-Pearson confidence intervals). SIRS = Systemic inflammatory response syndrome, qSOFA = (quick) Sequential Organ Failure Assessment, MEWS = Modified Early Warning Score.

undertreatment of sepsis. In our data, neither MEWS nor qSOFA seems to meet this criterion.

Finally, current guidelines for sepsis are not only aimed at early recognition but also at early treatment of sepsis. The Surviving Sepsis Campaign guidelines (2014) recommend to administer effective intravenous antibiotics within the first hour of recognition of severe sepsis and septic shock based on the SIRS criteria.[21] One of the main questions is whether the new sepsis definition is only meant for the recognition of patients with a higher risk of mortality or also as guideline for early antibiotic treatment. One year after the introduction of the new sepsis definition, many hospitals still use the SIRS criteria for the recognition of sepsis and severe sepsis on the ED. This is due to concerns of physicians that the strict selection of the qSOFA score may lead to undertreatment of sepsis and thus possibly increase its mortality.[22] Although no formal study has compared treatment regimens based on qSOFA to SIRS and MEWS, we share these concerns when looking at the drastic decrease in the number of patients who would be classified as septic in our ED.

Our study has a few limitations. First, a single-centre study was performed with a relative small number of patients compared with other recent studies. The number of randomised patients in our study was too low to detect small differences between the different sepsis scores. Particularly the low number of deaths in our cohort (only 12 patients with a probable infection) makes our sensitivity/specificity analysis less precise.

However, the small number of patients made detailed clinical follow-up possible of patients throughout their hospitalisation to confirm the presence of infection.

Another limitation is that only *medical* patients at the ED were included in this study. It is unknown whether the classification of sepsis by the different sepsis tools differs between medical patients and patients who suffer from other types of infections such as wound infections after surgery.

In summary, there are no major differences in gender, age, comorbidity and site of infection between patients with sepsis and severe sepsis classified by the SIRS, qSOFA criteria or a MEWS of ≥ 5 with a probable infection in the ED. However, the new qSOFA work-up for sepsis classifies only a very small group of patients with a higher mortality compared with the SIRS criteria. Due to this strict selection, the qSOFA score seems unsuitable as bedside tool in the sepsis work-up at the ED. Until the therapeutic implications of the qSOFA and the downstream effects on mortality have been formally evaluated in randomised clinical trials, the SIRS criteria upon which current knowledge about early treatment, particularly antibiotic treatment, of sepsis was founded should still be leading in the emergency department.

DISCLOSURES

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ORIGINAL ARTICLE

Outpatient clinic for users of anabolic androgenic steroids: an overview

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ABSTRACT

Background: Anabolic androgenic steroids (AAS) are used by approximately 20,000 amateur athletes in the Netherlands. AAS are harmful but data are lacking as to precisely how harmful they are. An outpatient clinic for past and current users of AAS was established in 2011 to acquire more knowledge about the health risks associated with AAS abuse.

Methods: All case files of the patients who visited the AAS clinic were reviewed retrospectively.

Results: 180 patients visited the AAS clinic between May 2011 and May 2016. Patients were strength athletes (99% male, mean age 34 years, range 19-61) who had started AAS use at a median age of 23 years (range 16-53). 95% used AAS in cycles (median of 4 cycles completed, median duration 10 weeks). Cycles consisted of a median of three different AAS, most commonly testosterone, nandrolone and trenbolone. Growth hormone was used by 34% in addition to AAS. Side effects occurred in 96% of patients, mainly acne (38%), gynaecomastia (34%) and agitation (27%) during cycles; decreased libido (34%) and erectile dysfunction (20%) afterwards. Medications regularly used by patients to self-treat side effects were aromatase inhibitors, clomiphene citrate, human choriogonadotropin, and tamoxifen.

Conclusion: AAS abuse did not lead to critical health issues. However, the incidence of less severe side effects among AAS users appears high. Considering the large number of abusers in the community, AAS abuse poses an important public health problem. A prospective study with a systematic approach is required to provide more reliable data regarding health risks of AAS abuse.

KEYWORDS

Anabolic androgenic steroids, AAS, performance enhancing drugs, PED, hypogonadism, bodybuilding, illicit drug use

INTRODUCTION

AAS abuse in the Netherlands

In the Netherlands approximately 160,000 people use performance enhancing drugs (PED), of which 20,000 anabolic androgen steroids (AAS).[1] Production and trading of AAS without a license is prohibited in the Netherlands, yet AAS can be easily acquired illegally through local dealers or the internet. The majority of users do not engage in organised sporting events.[1]

AAS is most often used intermittently, i.e. in cycles, and users' knowledge is based on information from acquaintances, trainers or the internet.[2] Among users, cycles differ greatly with respect to length, dosage as well as the number of different AAS used simultaneously or consecutively.[3] An earlier report showed that in about 50% of illegally obtained AAS the contents do not match the description on the label.[4] Therefore, it is difficult to attribute side effects to specific AAS or dosages.

Health concerns about AAS abuse

The Health Council of the Netherlands stated that AAS are harmful but data are lacking as to precisely how harmful they are.[5] Among physicians, there is low awareness of the possibility of AAS abuse by patients, and patients tend to be secretive about their use and do not rely on the physician's knowledge of AAS.[6] Knowledge of the unwanted somatic and psychological effects of AAS is limited because clinical research in the field of AAS is scarce. Prospective clinical trials among AAS users are hampered by ethical issues due to the fact that there is no registered indication for the use of supraphysiological doses of androgens, the products are mainly illegally obtained and most anabolic steroids are not registered for, nor extensively studied in, humans. As a result, most knowledge about the harmful effects of AAS is based on low level evidence, such as expert opinion, case reports or small observational studies.

Outpatient AAS clinic

An outpatient clinic for past and current users of AAS, the 'Anabolenpoli' or AAS clinic, was established in the Spaarne Gasthuis, Haarlem in 2011, in an attempt to gain more insight into the characteristics of AAS users, the methods of AAS use and the health risks associated with AAS abuse in the Netherlands. To our knowledge, it is the only clinic worldwide that focuses primarily on helping patients with health problems related to AAS. Patients need a referral to the clinic from their general practitioner or a medical specialist and the healthcare provided is fully covered by Dutch healthcare insurance. Haarlem is located centrally in the Netherlands with a maximum distance of 250 km to all country borders and is therefore readily reached by patients throughout the country.

The AAS clinic has now been running for five years. This study provides an overview of all patients who were referred to the clinic and generates novel data regarding recreational AAS use in the Netherlands and related health issues.

MATERIALS AND METHODS

Consultation at the AAS clinic

During consultation of each patient at the AAS clinic, the history of AAS use was assessed. Items discussed were the reasons for referral, the age at which the patient used AAS for the first time, the number of cycles completed, the number of years of active AAS use (every year with at least one cycle), and whether a patient had used continuously (defined as AAS use without interruptions for at least one year). Additionally, the types of AAS that a patient had used were inquired about as well as the use of other PED, medications to prevent or treat side effects, some of which are referred to as post-cycle therapy (PCT), with corresponding dosages. Patients were routinely asked which side effects were experienced during AAS use. All patients had a routine medical check including history and physical examination. If indicated, additional investigations were done, such as blood tests, urinalysis, semen analysis or electrocardiography.

Review of cases

For this study, all case files were reviewed for reasons for referral, patient and demographic characteristics, history and methods of AAS use, reported side effects, and use of other PED or medications. An overview was made of the investigations performed by the referring physicians as well as those ordered by the clinic, conclusions drawn and diagnoses established, and therapies employed. If available, follow-up data were recorded.

Descriptive analysis

Simple descriptive statistics were used to display quantitative data. If the variables were normally distributed, mean and standard deviation were calculated. If the distribution of a variable was skewed, a median is presented with a range. Documentation of the variables analysed was not complete in all case files. Data were frequently missing, for example for employment status, drug use or side effects. Therefore, percentages displayed in the results section (and tables) are not the percentages of all 180 patients but rather the percentage of patients from whom the data could be retrieved (numbers are indicated if applicable).

RESULTS

Patient characteristics

In total 180 patients visited the AAS clinic between May 2011 and May 2016. The number of patients referred annually was between 30 and 40. Patients came from municipalities throughout the Netherlands, and Belgium, as shown in *figure 1*. Patient characteristics are displayed in *table 1*. Patients had a mean age of 34 years (range 19-61) and 99% were male. The patients invariably engaged in physical strength sports, with 81% being former or current bodybuilders. Of the patients, 88% were not on AAS at the time of consultation. The reasons for referring a patient to the AAS clinic are presented in *table 2* and were related to symptoms occurring during or after a cycle (48%), suspected hypogonadism (10%) or abnormal blood tests (7%).

Figure 1. *Map of the Netherlands showing municipalities where patients lived when referred to the AAS clinic. The larger the green dot, the more patients coming from the corresponding municipality*

Table 1. *Patient characteristics*

Patient total	**n = 180**
Male	178 (99%)
Female	2 (1%)
Age (mean ±SD; range)	34 (±10.1; 19-61)
Occupational status	**n = 108**
Employed/working	72 (67%)
Student	12 (11%)
Unemployed	11 (10%)
Sick leave	7 (6%)
Disability benefit	3 (3%)
Welfare	3 (3%)
Recent drug use (other than nicotine/alcohol)	**n = 126**
XTC/speed	30 (24%)
Cocaine	28 (23%)
Cannabis	26 (21%)
GHB	23 (19%)
Sport (other than fitness/gym)	**n = 117**
Bodybuilding	95 (81%)
Combat sports (e.g. MMA, kickboxing, judo)	15 (13%)
Powerlifting	5 (4%)
Strongman athlete	2 (2%)
Current AAS use	**n = 180**
Not in cycles	158 (88%)
On cycles	4 (2%)
Bridging (i.e. AAS use in between cycles)	5 (3%)
Maintenance dose	13 (7%)

Numbers of patients and percentages are displayed in the right column, 'n' represents the number of subjects from whom the data could be retrieved. AAS = anabolic androgenic steroids.

Table 2. *Referring physicians and reasons for referral*

Referring physician	**n = 174**
General practitioner	126 (72%)
Internist	20 (11%)
Self-referral	16 (9%)
Psychiatrist	4 (2%)
Urologist	2 (1%)
Sports medicine physician	1 (1%)
Dermatologist	1 (1%)
Correctional medicine physician	1 (1%)
Fertility specialist	1 (1%)
Rheumatologist	1 (1%)
Sexologist	1 (1%)
Reasons for referral	**n = 180**
Symptoms during/after cycle	86 (48%)
• Decreased libido	20 (11%)
• Erectile dysfunction	16 (9%)
• Mood problems	13 (7%)
• Fatigue	13 (7%)
• Gynaecomastia	12 (7%)
• Subfertility	5 (3%)
• Palpitations	4 (2%)
• Anxiety	3 (2%)
• Derealisation	1 (1%)
• Acne	1 (1%)
• Wound infection	1 (1%)
• Other	14 (8%)
Abnormal blood tests	12 (7%)
• Polycythaemia	6 (3%)
• Proteinuria	3 (2%)
• Abnormal liver biochemistry	2 (1%)
• Elevated creatine kinase	1 (1%)
Suspected post-AAS hypogonadism	18 (10%)
Health check after AAS use	16 (9%)
Questions about AAS use	14 (8%)
Help/advice to abstain from AAS	12 (7%)
Other	22 (12%)

Some patients were referred for multiple symptoms. Numbers of patients and percentages are displayed in the right column. AAS = anabolic androgenic steroids.

METHODS OF USING AAS

Characteristics of AAS use by the patients and types of AAS used are summarised in *table 3*. The patients had a median age of 23 years (range 16-53) when they first used AAS. Of the patients, 94% used in cycles but 20% at some point used AAS uninterruptedly for more than 12 months. The number of cycles completed and the mean duration of a cycle per patient are shown in *figure 2*. Most visitors had completed more than three cycles prior to their visit. The duration of cycles varied considerably. However,

Table 3. *Characteristics of AAS use by the patients and types of AAS used*

Characteristics of AAS use	**Median (range)**
Age of first AAS use	23 (range 16-53)
Number of years of active AAS use	4 (range 1-35)
Number of cycles completed (see also *figure 2*)	4 (range 1-60)
Cycle length in weeks (see also *figure 2*)	10 (range 2-48)
Number of AAS in cycle	3 (range 1-10)
Cycles or continuous use	**n = 170**
Cycles (only)	135 (79%)
Continuous (only)	9 (5%)
Both	26 (15%)
Types of AAS used	**n = 177**
Testosterone	142 (80%)
• Testosterone enanthate	101 (57%)
• Testosterone mixture (i.e. Sustanon)	54 (31%)
• Testosterone propionate	28 (16%)
• Testosterone cypionate	12 (7%)
Nandrolone	118 (67%)
Trenbolone	113 (64%)
Stanozolol	111 (63%)
Boldenone	71 (40%)
Oxandrolone	46 (26%)
Methenolone	43 (24%)
Drostanolone	33 (19%)
Oxymetholone	24 (14%)
Mesterolone	14 (8%)
Dihydromethyltestosterone	3 (2%)
Dihydroepiandrosterone	1 (1%)

Medians with ranges and number of patients with percentages, respectively, are displayed in the right column. AAS = Anabolic androgenic steroids.

most cycles lasted between 6 and 18 weeks. Cycles mostly consisted of two or more different anabolic steroids. Products were used simultaneously or consecutively, and the dose, duration and combination of the different products used in the cycle differed substantially between cycles. Injectable testosterone esters were used by 80% of users, mostly combined with nandrolone, trenbolone, stanozolol and/or boldenone.

OTHER PED, MEDICATIONS AND PCT

Other substances used in addition to AAS are shown in *table 4*. Growth hormone was the most popular PED followed by clenbuterol and thyroid hormone. Medications used during or shortly after a cycle of AAS were aromatase inhibitors (anastrozole, exemestane and letrozole), anti-oestrogens (clomiphene citrate or tamoxifen), human choriogonadotropin (hCG), isotretinoin, sildenafil, diuretics and finasteride. Of the patients, 94 (71%) always used PCT following AAS use for a mean period of four weeks, whereas 28 (21%) patients never used PCT. Agents used in PCT were mainly tamoxifen, hCG and clomiphene citrate.

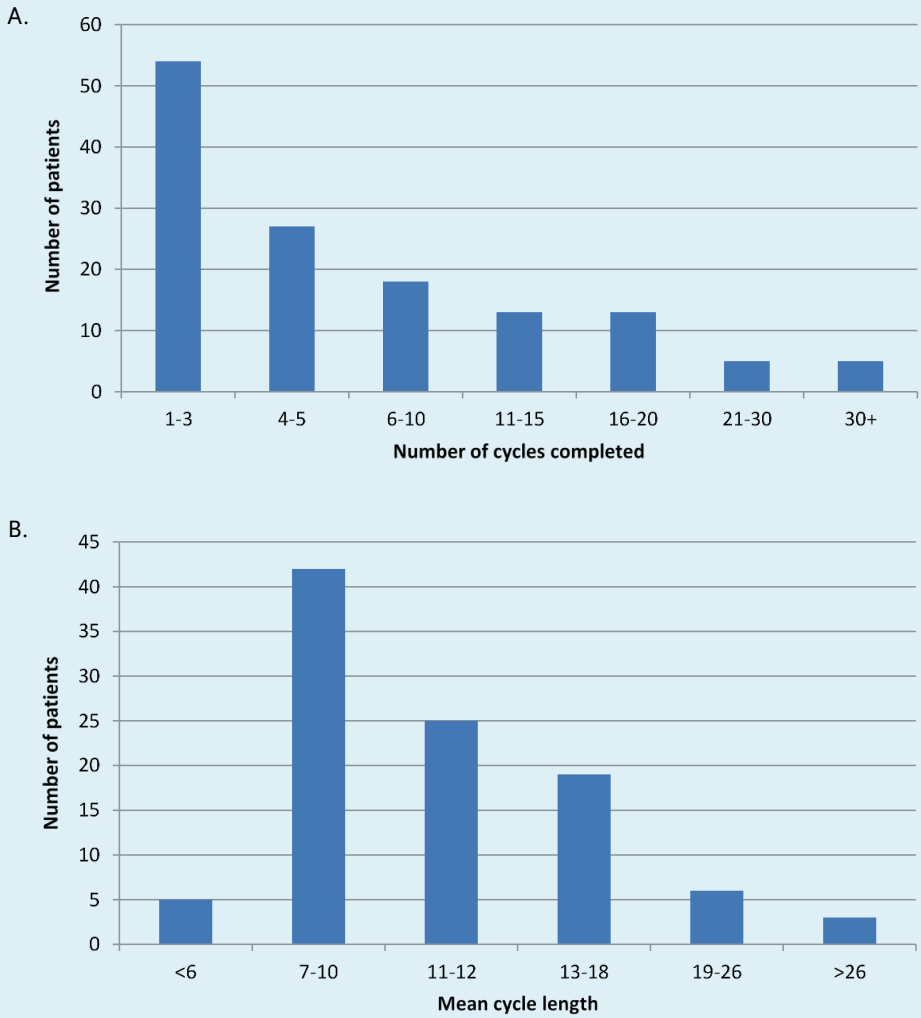
REPORTED SIDE EFFECTS

Of the patients, 96% reported at least one side effect attributed to the use of AAS *(table 5)*. Particularly common were acne, decreased libido, testicular atrophy and gynaecomastia. A general distinction could be made between side effects that occur during a cycle, i.e. gynaecomastia, fluid retention and aggressiveness, and those occurring after a cycle, i.e. erectile dysfunction and decreased libido. Of the reported health issues, none had led to hospital admission, except for a severe skin infection in one patient at an AAS injection site.

Additional investigations

If appropriate, additional tests were performed to investigate the relationship between reported health issues and AAS use. The results of blood tests, urinalysis and semen analysis are summarised in *table 6*. An elevated level of serum creatine kinase (CK) was observed in 45% of the tested patients. Of the six patients with a CK elevated 10 or more times the upper limit of the reference range, five were using or recently finished using AAS. The CK was restored to normal at repeat testing in the remaining patient. In one patient the liver biochemistry had been markedly abnormal during AAS use (7-8 times upper limit of ALAT reference range) but fully recovered when AAS were discontinued. An elevated plasma creatinine level (with a corresponding eGFR < 45 ml/min/1.73 m^2 calculated by the MDRD formula) was observed in two patients, of whom one had a previously diagnosed IgA nephropathy and the other used creatine ethyl ester (CEE) supplements daily. CEE is known to increase the plasma creatinine level, unrelated to kidney function.[7] After discontinuing the supplements, the creatinine level returned to normal. Polycythaemia (haematocrit > 55 %) occurred in four patients but was mild except for one patient who used a maintenance dose of Sustanon and required regular phlebotomy therapy.

Figure 2. *A. Bar chart of number of cycles completed by the patients. B. Bar chart of the mean cycle length (in weeks) performed by the patients*



Electrocardiography was performed in 24 patients and did not reveal any abnormalities except for one patient with positive voltage criteria for left ventricular hypertrophy. In one case, an MRI was performed to exclude a pituitary tumour as blood tests had revealed hyperprolactinaemia. In another case, karyotyping was used to demonstrate the Klinefelter syndrome as blood tests had showed hypergonadotropic hypogonadism which is not expected after current or previous AAS use. Furthermore, in one case hepatitis virus serology and liver ultrasound was performed to analyse abnormal liver biochemistry. No explanation was found but a relationship with AAS use was less likely as the liver enzymes remained elevated after discontinuation of AAS.

Diagnoses and treatment

Treatment of symptoms usually consisted of patient education, reassurance and advice. The general recommendation was not to use AAS again. Gynaecomastia was observed in 18 cases and treated with tamoxifen in eight but usually relapsed after discontinuation. In total six patients with gynaecomastia were referred to a plastic surgeon for extraction of breast tissue. Reduced fertility related to AAS use was diagnosed in five patients and treated temporarily with tamoxifen in two and hCG in one. There are no follow-up data to confirm whether treatment was effective in these patients except for the patient treated with hCG who did not recover. Azoospermia due to AAS was not seen. One case of infertility was explained as posttraumatic obstructive azoospermia. Temporary and long-term (> 1 year) post-AAS hypogonadism, defined as androgen deficiency due to AAS use, was established in 37 and 19 cases, respectively. Patients with long-term post-AAS hypogonadism had a significantly longer history of AAS use with a mean of 11 years compared with 6 years in the

Table 4. *Other performance-enhancing drugs, medications and post-cycle therapy used by patients*

Other performance-enhancing drugs	**n = 151**
Growth hormone	55 (36%)
Clenbuterol	46 (30%)
Thyroid hormone	35 (23%)
Ephedrine	2 (1%)
Medications (on-cycle)	**n = 151**
Aromatase inhibitors	20 (13%)
Human choriogonadotropin	19 (12%)
Clomiphene citrate	15 (10%)
Tamoxifen	14 (9%)
Isotretinoin	3 (2%)
Sildenafil	3 (2%)
Diuretics	2 (1%)
Finasteride	2 (1%)
Cabergoline	1 (1%)
Post-cycle therapy	**n = 151**
Tamoxifen	84 (56%)
Human choriogonadotropin	62 (41%)
Clomiphene citrate	49 (32%)
Aromatase inhibitors	11 (7%)
Mesterolone	4 (3%)

Numbers of patients and percentages are displayed in the right column.

rest of the patient population (unpaired t-test, p = 0.001). In 17 patients with post-AAS hypogonadism, tamoxifen was prescribed temporarily to enhance endogenous testosterone production. Testosterone substitution therapy was eventually instituted in 15 patients.

DISCUSSION

A total of 180 past or current AAS users visited the AAS clinic of the Spaarne Gasthuis in Haarlem, the Netherlands, between May 2011 and May 2016. The typical visitor to our clinic is a male, amateur strength athlete, who started using AAS in the second decade of life. Anabolic steroids are mostly used in cycles with a duration between 6 and 18 weeks. The unproven rationale behind this strategy is to gain muscle mass and strength during a cycle, allowing the body to recover between cycles. Since muscle mass and strength start to decline after discontinuation of AAS, multiple cycles or continuous use are deemed necessary to maintain or further increase the gained muscle mass. Some adopt the so-called 'blast and cruise' strategy, in which cycles with multiple high dose AAS are alternated with a lower maintenance dose. The contents, dose, and duration of the cycles are mostly directed by advice from self-proclaimed experts and are based on unproven beliefs and personal experience. AAS cycles are rarely identical, which shows that, although most users have strong beliefs about which type, dose and combination of AAS should be optimal for their purpose, there are no widely accepted guidelines. Most AAS cycles contain a type of injectable testosterone ester, generally combined with nandrolone, trenbolone and/or boldenone esters. Our findings are in concordance with questionnaire studies performed among bodybuilders

Table 5. *Side effects reported*

Reported side effect	**n = 160**
Acne	60 (38%)
Decreased libido	60 (38%)
Gynaecomastia	55 (34%)
Testicular atrophy	53 (33%)
Agitation	43 (27%)
Erectile dysfunction	32 (20%)
Mood problems	26 (16%)
Aggressiveness	18 (11%)
Fatigue	15 (9%)
Fluid retention	14 (9%)
Insomnia	10 (6%)
Diaphoresis	9 (6%)
Alopecia	8 (5%)
Infected site of injection	7 (4%)
Addictive behaviour	6 (4%)
Subfertility	4 (3%)
Syncope	3 (2%)
Pruritus	2 (1%)
Sleep apnoea	2 (1%)
Delusions	2 (1%)
Derealisation	1 (1%)
None	7 (4%)

The number of patients with corresponding percentages in whom these side effects occurred are displayed in the right column.

Table 6. *Additional tests performed and corresponding results*

Blood tests	**Definition**		**n = 152**
Elevated creatine kinase	CK > 170 U/l	1 - 3 x UL	34
		3 - 5 x UL	17
		5 - 10 x UL	11
		> 10 x UL	6
Abnormal liver biochemistry	ALAT > 45 U/l	1 - 2 x UL	27
		2 - 3 x UL	12
		3 - 4 x UL	5
		> 4 x UL	1
Androgen deficiency	< testosterone lower limit (variable)		53
Abnormal lipid profile	HDL-cholesterol < 0.9 mmol/l		32
Kidney damage	eGFR 45 - 60 ml/min/1.73 m²		7
	eGFR 30 - 45 ml/min/1.73 m²		1
	eGFR < 30 ml/min/1.73 m²		1
Polycythaemia	Haematocrit > 55%		4
Urine (dipstick) analysis			**n = 19**
No abnormalities			16
Proteinuria	+, ++, or +++		3
Semen analysis			**n = 9**
Normal fertility	Spermatozoa > 15 x 10^6/ml		3
Oligozoospermia	Spermatozoa < 15 x 10^6/ml		5
Azoospermia	Spermatozoa < 0.1 x 10^6/ml		1

The number of patients is displayed in the right column. Androgen deficiency was defined by a total and/or serum free testosterone level below the lower limit of the age-dependent reference range. Estimated glomerular filtration rate (eGFR) was calculated by the MDRD formula. UL = upper limit of reference range.

which found similar demographics and comparable characteristics of AAS use.[3,8] In addition to AAS, other substances are added, either to increase muscle mass (growth hormone) or to decrease fat mass (clenbuterol, thyroid hormone). Sometimes, medications are used to prevent or treat side effects during or after the cycle: aromatase inhibitors and tamoxifen (against gynecomastia and/or fluid retention), isotretinoin (to treat acne), human chorionic gonadotrophin (against testicular atrophy and/or reduced fertility), sildenafil (to treat erectile dysfunction) or finasteride (to prevent hair loss). As a result of prolonged AAS use, endogenous testosterone production and spermatogenesis are suppressed during and for weeks after the cycle. In an attempt to speed up hormonal recovery as well as to prevent symptoms of androgen withdrawal, most users take post-cycle therapy. PCT mostly consists of a combination of tamoxifen, clomiphene or hCG, usually taken for 2-4 weeks shortly after the end of the cycle with AAS. Although widely used, the efficacy of PCT remains to be determined.

Health risks of AAS abuse

There are several reasons why users of AAS may have an increased risk of health problems. Firstly, most of them fanatically engage in weight training which may lead to symptoms resulting from overburdened muscles, joints and tendons. Secondly, a considerable number of the visitors of our clinic admitted to using drugs, such as XTC, cocaine, cannabis and GHB. The high incidence of recent drug use has been reported previously. Survey studies showed that 23-33% of AAS users meet the criteria for substance dependence disorder compared with 11% of non-AAS users.[3,9-11] Most importantly, the use of high-dose androgens and associated substances to treat side effects may have adverse effects. In our 180 patients no critical health issues occurred. The most severe

complication was a serious skin infection at the injection site. The large majority of our subjects nevertheless reported one or more side effects related to the use of AAS. The side effects and their frequency of occurrence correlate with those described in earlier studies.[8,12,13] Most users were familiar with common side effects such as acne, gynaecomastia, testicular atrophy, fluid retention, agitation and fluctuations in libido and regarded them as inherent to the use of these substances. Most of these side effects were rated by them as mild or temporary and acceptable with respect to the perceived increase in muscle size and strength. A substantial proportion of the reasons for referral to our clinic were related to these side effects, especially when they persisted after discontinuation of the AAS. Side effects that may go undetected by the patient include high blood pressure, abnormal liver biochemistry, polycythaemia, decreased HDL-cholesterol and decreased sperm count. Whereas high blood pressure and polycythaemia were rare findings in our population, lower HDL-cholesterol was frequently encountered. Although low HDL-cholesterol is associated with an increased risk of cardiovascular disease in the general population, it is unclear if and to what magnitude this contributes to cardiovascular morbidity in AAS users, knowing that a decreased HDL-cholesterol may be transient. Mild elevation of aspartate transaminase (ASAT) and alanine transaminase (ALAT) was a common finding in our subjects. Cholestatic liver damage is associated with use of oral AAS, since these compounds are alkylated to prevent extensive metabolism in the liver.[14] However, we believe that in most cases, mild elevation of ASAT and ALAT is not a sign of liver damage, but is due to muscle damage associated with extensive strength training. This is also suggested by a clearly elevated level of CK and normal levels of alkaline phosphatase and γ-glutamyltransferase in most subjects. Low sperm count results from suppression of the hypothalamo-pituitary-gonad axis during AAS use. Since supraphysiological doses of AAS are used, suppression of luteinising hormone (LH) and follicle-stimulating hormone (FSH) to levels below the limit of detection is inevitable. From male hormonal contraception studies it is known that it may take up to six months after the first injection of testosterone until sperm counts have decreased to 1 million/ml and that the magnitude of suppression may vary between men.[15] Both the extent of suppression and time to recovery of spermatogenesis will likely depend on the dose of AAS and cycle length. In our study we only performed semen analysis in the few cases in which reduced fertility was the reason for referral. Moreover, we did not have pre-cycle semen tests. Therefore we were unable to establish a causal relationship between AAS use and impaired semen quality.

Treatment of patients

Persisting side effects despite discontinuation of AAS were the most common reason for referral to the AAS clinic. Mostly, side effects were related to the (perceived) disturbance of male gonadal function, resulting in gynaecomastia, erectile dysfunction, loss of libido and a range of less circumscribed symptoms that may be attributed to low testosterone levels. In most cases reassurance and advice to be patient about spontaneous relief of symptoms was sufficient. Persistent, painful gynaecomastia was treated with tamoxifen 20 mg daily. Although this relieved symptoms in the majority of cases, the chance of recurrence after cessation of therapy appeared to be high. Eventually, many patients chose surgery as a definitive treatment. Post-AAS hypogonadism usually resolved without therapy within six months after the last injection of AAS. Testosterone substitution therapy was reserved for patients with long-term post-AAS hypogonadism who were motivated to stop AAS indefinitely and had a significant symptom burden. It appeared that particularly the subjects with a high cumulative dose of AAS abuse were at increased risk of long-term suppression of endogenous testosterone production. In these cases, endogenous testosterone levels were repeatedly slightly below or above the lower limit for young men and associated with symptoms such as erectile dysfunction, loss of libido, fatigue and depressed mood. A particular drawback of testosterone treatment is that it stops recovery of the function of the hypothalamo-pituitary gonad axis. Especially when adequate spermatogenesis is important, a trial with tamoxifen 20 mg daily may be indicated instead. Tamoxifen acts as an oestrogen antagonist on the hypothalamus and pituitary and stimulates LH and FSH release by the pituitary. In our experience it mildly increases endogenous testosterone production and spermatogenesis. However, in most men the testosterone levels decreased to the pre-treatment levels after stopping tamoxifen. When tamoxifen is not sufficient, hCG 1500 IU twice weekly mostly results in normalisation of endogenous testosterone levels within weeks, followed by restoration of sperm concentration within months.

Limitations of the study

Our study has a few important limitations. Although our clinic is the only clinic dedicated to AAS in the Netherlands, it only provides care for a small minority of the total group of AAS users. It presents a selection of people who were referred or self-referred because of side effects or problematic AAS abuse. Users without health issues would not consult the AAS clinic, therefore the estimated incidence of side effects in our study is probably exaggerated. Similarly, since only users with

health problems were selected, their method of use may have been more hazardous. We were unable to verify the concentration and contents of the substances used by our patients. Evaluation, treatment and follow-up of the subjects were not standardised. Patients were either past or current users, and the time between last AAS use and evaluation varied extensively. The current study is retrospective in nature and documentation was incomplete on many items. The documented percentages of types of AAS, PED and medications used as well as side effects reported are likely to be affected by recall bias and reporting bias. Additionally, we were unable to establish a causal relationship between AAS abuse and health issues or abnormal laboratory tests.

Nonetheless, this study is so far the most elaborate to be conducted in the Netherlands. Patients came from all over the country. Our experience with AAS users in the clinic and comparison with literature data have led us to believe that patient characteristics and the mode of AAS use as described in our study is representative for AAS abuse in general. We therefore believe this study gives a good insight into the practice of AAS abuse and its most common side effects and health risks.

Concluding remarks

This review of 180 patients referred to the AAS clinic suggests that AAS abuse does not structurally lead to severe health problems and critical side effects are limited to incidental cases as reported in literature. However, the incidence of side effects with a substantial symptom burden, reduced fertility, substance abuse dependence and potentially harmful concomitant use of other PED and medications among AAS users is high. Considering the large number of users in the community, AAS abuse may be an important public health problem.[13] A prospective study with a systematic approach is required to provide more reliable data regarding short- and long-term health risks of AAS abuse. Moreover, we need clinical trials to study the efficacy and long-term effects of treatment.

DISCLOSURES

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ORIGINAL ARTICLE

An alternative ICU staffing model: implementation of the non-physician provider

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ABSTRACT

Introduction: Literature in Europe regarding implementation of nurse practitioners or physician assistants in the intensive care unit (ICU) is lacking, while some available studies indicate that this concept can improve the quality of care and overcome physician shortages on ICUs. The aim of this study is to provide insight on how a Dutch ICU implemented non-physician providers (NPP), besides residents, and what this staffing model adds to the care on the ICU.

Methods: This paper defines the training course and job description of NPPs on a Dutch ICU. It describes the number and quality of invasive interventions performed by NPPs, residents, and intensivists during the years 2015 and 2016. Salary scales of NPPs and residents are provided to describe potential cost-effectiveness.

Results: The tasks of NPPs on the ICU are equal to those of the residents. Analysis of the invasive interventions performed by NPPs showed an incidence of central venous catheter insertion for NPPs of 20 per fulltime equivalent (FTE) and for residents 4.3 per FTE in one year. For arterial catheters the NPP inserted 61.7 per FTE and the residents inserted 11.8 per FTE. The complication rate of both groups was in line with recent literature. Regarding their salary: after five years in service an NPP earns more than a starting resident.

Conclusion: This is the first European study which describes the role of NPPs on the ICU and shows that practical interventions normally performed by physicians can be performed with equal safety and quality by NPPs.

KEYWORDS

Intensive care, invasive procedures, non-physician provider, nurse practitioner, physician assistant, cost-effectiveness

INTRODUCTION

Both the scale at which nurse practitioners (NP) and physician assistants (PA) are implemented and their exact tasks and responsibilities on the intensive care units (ICUs) throughout Europe remain unclear. Nevertheless, these non-physician providers are already employed with equal competences to residents in some ICUs in European countries. Although implemented in ICU staff, European literature on this subject is lacking, with the only research being conducted in the United States of America (USA).

Available research from the USA shows that from 1960 until the 1990s the NP as well as the PA were implemented in the ICU. Back then, they were mainly introduced in regions with physician shortage to execute the tasks normally done by resident physicians. Their role was based on a natural evolvement from registered nurse in the ICU to an acute care nurse practitioner (ACNP) who could provide the necessary medical care for patients. Because the ACNP became indispensable on several American ICUs and emergency departments, the ACNP received a legislated title in the 1990s.

In 2008 the review by Kleinpell et al. concluded that ACNPs and PAs on the ICU provided high-quality care which was non-inferior to that of residents.[1] The ICU length of stay (LOS) and mortality were comparable if patients were treated by teams with ACNPs and an intensivist or by teams consisting of residents or fellows and an intensivist. In contrast to the non-inferiority, the advantage of ACNPs was their continuity of care and an experienced ACNP needed less supervision from intensivists compared with residents doing an internship. Moreover, a review of 2012 by Edkins et al. revealed that ACNPs provided high-quality care at a low cost.[2]

Around the year 2000, the general concept of NPs and PAs in medicine and their training course was also recognised in the Netherlands because of an expected increase in

healthcare demand as a result of economic welfare and the ageing population.[3] They were also implemented in some ICUs. Although the function of NPs and PAs on the ICU is similar to the tasks performed by ACNPs, ACNPs mostly cover a broader part of acute care and their comparable legislated title has not yet been introduced in the Netherlands. The theoretical and practical skills of the NPs and PAs on the ICU, however, are comparable with those of ACNPs and similar to the job description of residents on the ICU. Therefore, the more generally accepted term 'acute non-physician providers (NPP)' will be used in this article to refer to NPs and PAs working on the ICU.

The aim of this paper is to describe the course of training and implementation of an alternative ICU staffing model with NPPs besides residents and intensivists in the Netherlands. In addition, a description of the invasive procedures performed by NPPs, residents or intensivists is reported with a retrospective cohort analysis to provide some insights on the quality of care and one of the tasks of NPPs on a high volume ICU in the Netherlands.

METHODS

Setting

Catharina Hospital is a tertiary hospital in Eindhoven, the Netherlands containing all medical specialties, except for complex neurosurgical patients who require intensive care admission. The hospital has a 33-bed mixed medical and surgical ICU and provides care as a referral centre for the region with the characteristics described in *table 1*. The medical staff of the ICU consists of intensivists, 8.8 fulltime-equivalent (FTE), supported by residents, residents in training and NPPs for which the FTEs are reported in *table 2*. Residents in training are on a rotating schedule of 3 to 4 months in which ICU experience is mandatory for their specialist training. The weekly required hours for residents, residents in training and NPPs are equal and 38 hours per week according to a local agreement.

The nurse practitioner training course

For ten years now, the training program to obtain a master degree of acute care nurse practitioner (NP) is available in Catharina Hospital together with Fontys University of Applied Sciences. A minimum of four years' experience as an ICU nurse was arbitrarily chosen as a local requirement to be eligible for the acute care NP training as a certain settlement in and acknowledgement from the nursing group is required to attain the supervising role of an acute care NP. In 2016 the NP training consisted of theoretical medical skills, practical skills and nursing skills. For the theoretical medical skills, participants are trained in clinical reasoning based on broad medical and pathophysiological insights to create differential diagnoses. The nursing part includes training in nursing diagnosis, such as recognising problems like fear, discomfort and decubitus combined with the aim to prevent these problems. The practical part consists of two years of hands-on clinical physician work on the ICU, like the resident physicians, with the focus on the different medical specialties and their problems. After graduation, the acute care NP has the same job description and responsibilities as the resident.

The physician assistant training course

In contrast to the NP training course, the physician assistant (PA) training course is more focused on the medical domain and consists of a theoretical part, which attends to medical problems in all specialties from

Table 1. *Baseline characteristics of ICU patients in the two study years*

	2015	2016
No of admissions	2922	2935
Age	65.6 (SD 12.5)	65.8 (SD 12.6)
SAPS II	34.9 (SD 18.3)	33.5 (SD 16.9)
Mortality in ICU	5.1%	4.5%
Mortality in hospital	8.3%	4.2%
Standardised mortality ratio Apache IV	0.50	0.54
Standardised mortality ratio SAPS II	0.39	0.46
Length of stay on ICU, mean	2.5 days	2.7 days
Length of stay on ICU, median	1.1 days	1.1 days

Table 2. *ICU experience of residents, residents in training and NPPs in 2015 and 2016*

	ICU experience	Residents (FTE)	Residents in training (FTE)	NPPs (FTE)
2015	< 1 year	10.00	1.75	
	> 1 year	1.50	1.00	
	> 2 years			4.28
2016	< 1 year	7.50	3.55	
	> 1 year	1.00	0.16	
	> 2 years			3.60

psychiatry, surgery to internal medicine. The participants are assessed with multiple station exams in which the participant has to solve clinical problems, propose therapies and prescribe medication. The practical part consists of hands-on training on the ICU and traineeships within several specialties. Graduation also results in a master degree with the same job description as the residents in the ICU. This course is also provided in Catharina Hospital together with HAN University of Applied Sciences.

Job description

Both the NP and the PA master degrees grant permission to legally perform medical care on the ICU, such as making treatment plans including prescribing treatment medication, presenting at multidisciplinary meetings, and performing invasive procedures. A specialist always supervises these tasks, which in this case is an intensivist. There is no difference in practice between the NPs and PAs on the ICU. Both have the same competences and tasks as all residents on the ICU. These NPPs perform some extra tasks such as improving local ICU protocols and, like intensivists, they are also involved in guiding new residents, as mentors, during their first month on the ICU to familiarise them with the ICU and protocols.

In Catharina Hospital, the day shift of NPPs is made up of various components, which start with a morning handover. After this collective handover the NPPs and residents start off with the clinical examination of the admitted ICU patients. Both NPPs and residents compose an initial treatment plan with optional additional examinations based on their findings. This proposed plan is assessed and adjusted, if necessary, by the intensivist during the ward round at the end of the morning. In the beginning of the afternoon the NPPs and residents report the main problems with the initiated treatment of all admitted patients in a multidisciplinary meeting containing representatives of all relevant specialties and three intensivists. After this meeting the NPPs and residents take care of the additional requested examinations, check all prescribed medication and communicate with family. If necessary, the NPPs or residents can perform invasive procedures, such as insertion of central venous or arterial lines, thoracotomies with tube insertion, intubations and electro-cardioversion. Only arterial lines or peripheral venous catheters are placed without supervision of the intensivist if the NPP or resident who is taking care of the patient is confident enough. If not confident or in case of one of the other interventions, the intensivist decides whether the invasive procedure needs to be supervised based on the characteristics of the patient and the NPPs' or residents' experience and his or her confidence. Supervision ranges from observation to hands-on guidance. All upper central venous accesses are performed by either the intensivist or NPP since residents have limited experience in placing upper central venous catheters. Ultrasound for additional guidance is used when deemed necessary. The day shift ends after eight hours with a handover. Two NPPs, two residents, or one NPP and one resident cover the eight-hour shifts of the evening and night. Those in attendance are responsible for all admitted ICU patients, resolve problems that may emerge and can perform invasive procedures. Besides these duties during these shifts, both NPPs and residents are part of the rapid response team in Catharina Hospital.

Data collection and analyses

Since 2015, all patients undergoing an invasive procedure by an NPP are entered in the quality database of NPPs. The data of 2015 and 2016 were extracted and loaded into Microsoft Excel 2013 in an anonymised manner. Since 2016 the inserted central venous or arterial catheters on the ICU, which are entered in a central hospital database to monitor the number the catheter-related bloodstream infections, could be attributed to either residents together with intensivists or NPPs. All these databases are prospective databases with variables such as medical history, relevant medical scoring systems, the diagnosis, complications and interventions. After extracting these data and comparing them with the separate NPPs' quality database, the study group was able to recognise which catheters were inserted by the group of NPPs or inserted by the group of residents and intensivists, or by intensivists in case of upper central venous lines during 2016. It was only possible to determine if a catheter was inserted with or without the supervision of an intensivist for catheters inserted by the NPPs. For the group of residents and intensivists it was not possible to determine whether a venous or arterial catheter was inserted by either the intensivist or the resident, or by the residents with supervision of the intensivist. However, arterial catheters are mostly inserted without supervision by either NPPs or residents and not by intensivists. The number of inserted catheters was plotted against the fulltime-equivalent (FTE). An ultrasound was available for guidance and its use depended on the preference of the person placing the line combined with patient characteristics.

Because of the descriptive nature of this study we collected a diverse amount of outcomes of interest. First of all the baseline characteristics of the ICU in 2015 and 2016 were collected to give an overview of the general ICU performance and the ICU population. The collected baseline characteristics were age, Simplified Acute Physiology Score (SAPS II), ICU and hospital mortality, standardised mortality ratio correct for the APACHE IV score and the SAPS II, and the length of stay on the ICU and in the hospital. Second, the number and device characteristics of documented invasive procedures combined with the number of procedural complications for

central venous catheter (CVC) insertions were recorded. The included invasive procedures were insertion of central venous or arterial catheters, thoracotomies with tube insertion, intubations and electro-cardioversion. Procedural complications were pneumothorax, recognised on chest radiograph; major bleeding, defined as bleeding causing haemodynamic instability or endangering vascularisation of the limbs; catheter-related bloodstream infections (CLABSI), defined as a primary bloodstream infection in a patient who had a central catheter inserted within the 48-hour period before the developing the infection and that is not bloodstream related to an infection at another site;[4] and malposition based on the upper CVC defined as tip placement in the distal portion of the superior vena cava just above the junction with the right atrium (cardiac silhouette) as judged by a radiologist.

To gain insight into the costs of NPPs and residents, the salary scales of both were adapted from the collective hospital labour agreement of the Dutch Hospital Association (*table 3*). The FTE for residents, residents in training, and NPPs on the ICU in Catharina Hospital was equal and consists of 38 hours a week.

Statistical analysis

Statistical analysis was performed with Microsoft Excel 2013. The data for this retrospective cohort study are described as numbers or percentages or given as a mean with standard deviation. A median and interquartile range are shown if the data were not normally distributed.

RESULTS

The baseline characteristics of all admitted ICU patients in 2015 and 2016 are summarised in *table 1*. The number of admissions, mean age, SAPS II, standardised mortality ratios and length of stay were alike for both years.

In 2015 and 2016, NPPs performed 251 and 407 invasive procedures, which were 58.6 and 113.1 procedures per FTE, respectively. *Figure 1* shows the distribution of all invasive procedures that were performed by the NPPs for 2015 and 2016. *Figure 2* demonstrates the distribution for which CVCs and which arterial catheters were performed by unsupervised NPPs, by residents supervised by NPPs, by NPPs supervised by intensivists, and by residents or intensivists in 2016. The total number of CVCs inserted by NPPs and physicians together in 2016 was 125. Of these CVCs, 58% (n = 73) were inserted by or under supervision of NPPs, while 42% (n = 52) were inserted by residents or intensivists or by an NPP supervised by an intensivist (*figure 2*). The incidence of CVC insertions by NPPs was 20 per FTE, while the incidence of CVC insertion by residents, with or without supervision, was 4.3 per FTE and 2.5 per FTE if the 8.8 FTEs of the intensivists were taken into account along with the residents.

The incidence of inserting arterial catheters combined with supervising arterial cannulation all by NPPs was 61.7 per FTE and if the rest of the arterial catheter insertions were distributed over only residents the incidence was 11.8 per FTE. When both the FTEs of intensivists and residents are taken into account, this incidence becomes 6.9 per FTE.

Both the number of intubations and thoracotomies by NPPs increased in 2016 compared with 2015. The increased number of thoracotomies was explained by the fact that most NPPs became self-dependent in performing this procedure. In 2015 only the complication rate of CVCs inserted by NPPs was available; there were two misplacements and one failure to place. Of all invasive procedures with CVCs, there were five complications for NPPs and intensivists together in 2016, all while placing upper CVCs. There was one pneumothorax caused by an NPP during insertion of a subclavian catheter. There was one CLABSI 14 days after insertion of a CVC by an NPP. Three complications arose during attempts to insert a CVC by an intensivist in one single patient. There was a pneumothorax and mediastinal bleeding after an attempt of placement of a subclavian catheter. After this attempt an ultrasound guided jugular catheter was inserted too deep (in the right atrium). The data over 2015 and 2016 for NPPs showed two misplacements, one failure to place and one pneumothorax. There were no other complications during the invasive procedures documented.

The salary scale of NPPs and residents is depicted in *table 3*. The payment in Euros represents the salary per month. The increments of salary are represented by the numbers in the first column and increase once per working year.

DISCUSSION

This descriptive study shows how intensive care nurses can be successfully trained locally, based on a university program, and be implemented as NPPs on the ICU. The included retrospective cohort analysis demonstrates that NPPs perform more invasive line insertions per FTE than intensivists or residents, with a complication rate that is up to standard and comparable with that of the intensivist. These findings show that implementation of NPPs can result in a reduction in the workload of intensivists who can then allocate time to other tasks. In addition, both the NPPs' experience and thorough knowledge of the ICU may add a quality impulse to ICU care.

Although the results of this descriptive study may indicate a beneficial role for NPPs on the ICU, the concept of an NPP in the Netherlands and Europe remains

Figure 1. *Graph: invasive procedures by NPs and PAs in 2015-2016*

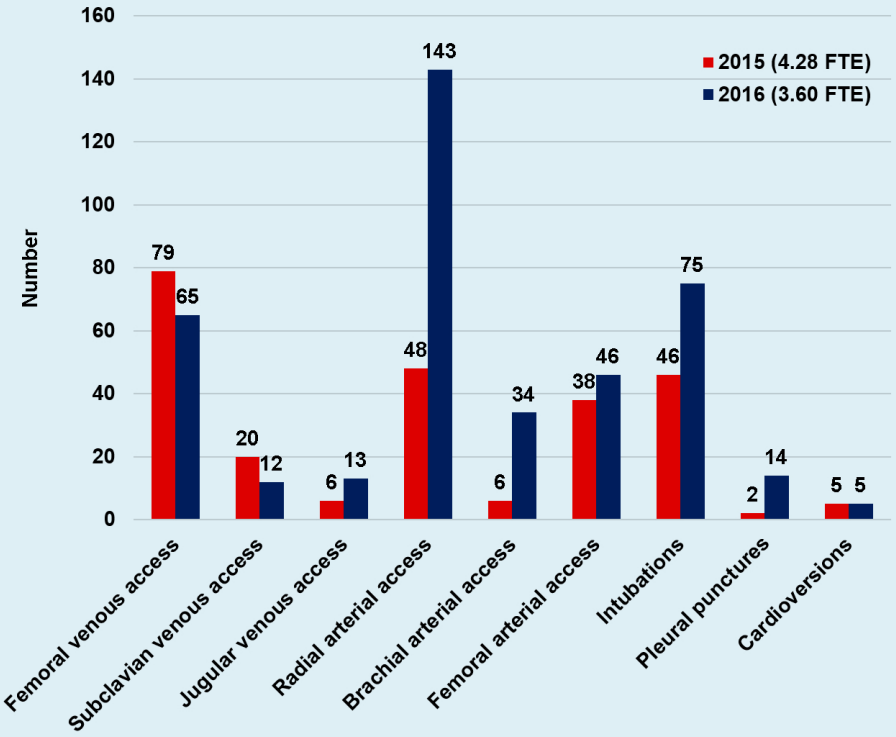
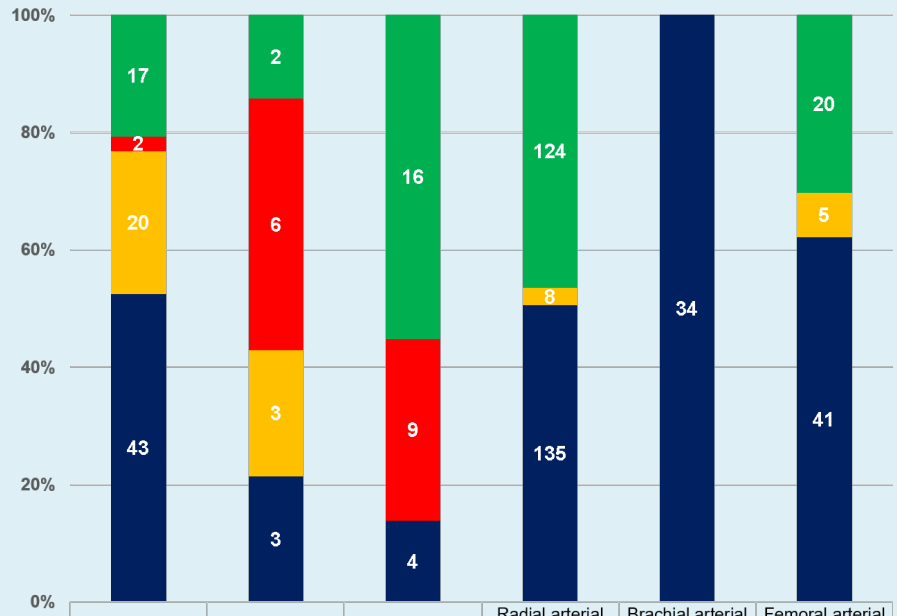


Figure 2. *Graph: NPs and PAs vs residents in 2016, all vascular access is shown in percentages (bars)*



	Femoral CVL	Subclavian CVL	Jugular CVL	Radial arterial line	Brachial arterial line	Femoral arterial line
Intensivist or resident supervised by intensivist	17	2	16	124	0	20
NP supervised by Intensivist	2	6	9	0	0	0
Resident supervised by NP	20	3	0	8	0	5
NP unsupervised	43	3	4	135	34	41

relatively unknown. There is no Dutch or European medical evidence available describing the role and potential advantages of NPPs on the ICU. This lack of literature is becoming increasingly important; such evidence may even be essential, since ICU medicine and therefore ICUs are undergoing change. Nowadays, Dutch intensivists mainly work in a closed format which means that they have the final responsibility for their ICU patients and their daily treatment plans. They base their treatment on their own knowledge combined with the advice requested from other specialists. Compared with the earlier days of the ICU, where the surgeon, internist or other specialists treated the patient on the ICU, this change has improved the quality of care, but also intensified the workload on the ICU. NPPs may be a viable staffing alternative to achieve the goal of managing increasing workloads while retaining a high quality of care.

In the foreseeable future more changes can be expected, such as a physician shortage due to advances in complex medical techniques, the increasing age of ICU patients and migration of physicians to cities.[5,6] Some rural areas of Europe are already coping with physician shortage.[7-9] Although there is not yet a shortage of intensivists in the Netherlands, finding nurses and residents to cover 24/7 shifts on the ICU is becoming more difficult due to duty hour restrictions of residents and the desire to work in specific areas of the country.

Moreover, the quality of care of residents on the ICU could be organised more efficiently. For most residents the ICU internship is their first encounter with ICU care. Their time for acquiring knowledge and experience in this area mostly remains limited due to their rotating internships for the specialist training. Training of these residents consumes time and the quality improvement of this training on ICU care only becomes noticeable at the end of their internship. Both reasons, the availability of residents and their limited experience, affect the continuity and quality of daily ICU care and may provide opportunities for the NPP.

Both residents and NPPs require training and supervision by intensivists. While the training to become an NPP takes longer, a reasonable assumption is that in the end residents require more training time and supervision as they consist of a larger group, generally have no ICU experience, and continuously rotate after a mean of 3-4 months resulting in limited time to profit from their acquired experience. In addition, since NPPs already worked on the ICU as nurses they know the local protocols and require less supervision from the intensivists. This knowledge even makes it possible for them to guide the new residents on the ICU by explaining local protocols and training or supervising the more simple interventions.

Table 3. *Salary scale of the NPP and of the resident*

Salary scale	NPP	Resident
1	€ 2960	€ 3363
2	€ 3097	€ 3490
3	€ 3227	€ 3636
4	€ 3363	€ 3774
5	€ 3490	€ 3917
6	€ 3636	€ 4054
7	€ 3774	€ 4177
8	€ 3917	€ 4303
9	€ 4054	€ 4431
10	€ 4115	€ 4557
11	€ 4177	€ 4684
12	€ 4241	€ 4812

The second part of this descriptive study underscores a potential advantage of implementing NPPs by describing routine invasive procedures in the ICU. The number of inserted venous and arterial catheters per FTE was higher for NPPs (CVC: 20/FTE, arterial catheters 61.7/FTE) than for residents and intensivists together (CVC: 4.3/FTE, arterial catheters: 11.8/FTE). Although information bias could have influenced these numbers, the hypothesis could be that these numbers are due to NPPs not being subjected to time limited experience on the ICU, in contrast to the residents. This experience results in their capability to insert venous and arterial catheters without the supervision of an intensivist. Our observed complication rate of the NPP data from 2015 and 2016 was in line with the study by Alexandrou et al. Their comparable complication rate during a 13-year follow-up of a catheter insertion service executed by non-physicians of the ICU is up to the international standards.[10-12] Moreover, *figure 2* shows that NPPs are indeed able to educate and supervise residents in our hospital. These examples indicate that NPPs can facilitate a broader span of control of the intensivist by taking over some of the tasks with the same quality of care. A further advantage of this workflow is centralisation of these interventions, which is in line with the observed success and complication rate.

American literature already supports implementation of NPPs by reporting a quality impulse on several aspects of ICU care. Both mortality and length of stay on the ICU and in the hospital remain the same or are even slightly better in cohorts of ICUs with NPPs compared

with ICUs staffed by only residents and intensivists.[13-17] Additionally, one study analysed the communication between nurses, non-physicians and physicians and found a satisfactory communication of NPPs by all groups and a better communication of NPPs than physicians from the perspective of some groups.[18]

This is in line with the study by Rayo et al. which suggests better comprehended hand-overs and patient orders by experienced NPPs compared with new residents.[19] These results refer to the problems residents encounter on the ICU in terms of understanding and carrying out orders during multidisciplinary meetings.[20] Both outcomes can be explained by ICU-NPPs being more experienced in protocols, routine ICU processes and familiarity with patient orders on the ICU than most residents.

All these benefits can provide improved continuity of quality for care on ICUs, which is the primary reason for considering implementing NPPs. Whether this quality improvement by NPPs is also cost-effective remains an unanswered question. Although several studies address this question, it remains difficult to extrapolate their results to other ICUs, as the workflow in each ICU can differ significantly. However, one can hypothesise that outsourcing several tasks of an intensivist to a more inexpensive NPP can save intensivists time and be cost-effective. Based on the plain salaries, NPPs cost more than residents in the long term. The extra costs come with the potential benefit of quality improvement as a result of the NPPs' continuity and experience on the ICU.

Limitations

The most important limitations are inherent to the retrospective cohort design of this study and description of one single ICU. The first limitation is selection bias as the more difficult invasive interventions are more likely to be done by the most experienced person available, so the NPP or the intensivist. This could explain the higher number of interventions performed by the NPPs compared with residents. It can also overestimate the number of complications caused by intensivists as they potentially had to insert upper CVCs in more sick or less technically accessible patients.

Considering the data collection, retrieving data on catheter insertions performed by residents or intensivists was only possible in the year 2016, while NPPs' data could be obtained over the years 2015 and 2016. Moreover, the aggregated data of intensivists and residents made a desired in-depth comparison between residents and NPPs impossible. Additionally, the second bias is the information bias. This could underestimate the number of performed interventions of residents as in our experience they underreport interventions more often since they do not have a separate database. Co-intervention bias is a third possible bias as potentially one group could have increased the use of ultrasound in the analysed years.

Comparability between residents and NPPs remains difficult. In general, residents have less ICU experience than NPPs due to their shorter presence on the ICU. In contrast, this limited time and therefore experience are also one of the main reasons for considering implementation of NPPs. Their continuity, experience and knowledge of ICU processes is the main advantage.

Finally, this study describes a training course and staffing model with NPPs in one single centre and therefore results can be different in other ICUs with other case mixes.

CONCLUSION

This descriptive report covers a successful local method of implementing NPPs on the ICU, as a new staffing model concept in Europe. To provide insight on the quality of their skills, an included retrospective cohort analysis indicates that the quality of invasive procedures with a low complication rate seems comparable between NPPs, and residents and intensivists. Whether sustainable quality improvement can be achieved with NPPs in the ICU setting should be subject to further study, both in the Netherlands and in Europe.

DISCLOSURES

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ORIGINAL ARTICLE

Familiarity of general practitioners with Q fever decreases hospitalisation risk

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ABSTRACT

Introduction: Between 2007 and 2010, the Netherlands experienced large outbreaks of Q fever with over 4000 cases. There were unexplained geographical differences in hospitalisation rates of notified patients. We examined the extent of this geographic variation in Q fever hospitalisation and its potential association with general practitioner (GP) experience with Q fever.

Methods: We included Q fever cases notified by GPs in 2008 and 2009 in the affected public health region. We used linear regression to describe trends of hospitalisation over time and tested for statistical differences in hospitalisation between municipalities with the chi-square test. We used the number of previously diagnosed Q fever cases of an individual GP as a proxy for Q fever experience, grouped into four categories of GP experience (1; 2; 3-7 and 8 or more cases). We calculated adjusted odds ratios (OR) using logistic regression, taking into account clustering at the GP level.

Results: The proportion of hospitalised cases was highly variable between municipalities (range 0-56%, p-value < 0.001). The proportion of hospitalised cases decreased monthly by 0.7% (95% confidence interval (CI): 0.03-1.3%). The risk of hospitalisation was lower when GPs had seen eight or more Q fever cases compared with GPs who had seen only one case (OR 0.4 [95% CI: 0.2-0.8]).

Discussion: Our findings suggest that increased GP experience was associated with a reduction in hospitalisations. This supports the public health initiatives to disseminate epidemiological updates and information regarding diagnostic and therapeutic options for Q fever to GPs to reduce Q fever related hospitalisation.

KEYWORDS

Coxiella burnetii, general practitioners, hospitalisation risk, Q fever

INTRODUCTION

Q fever is a zoonosis caused by the bacterium *Coxiella burnetii* which occurs worldwide.[1] Approximately 40% of infections with *C. burnetii* result in clinical symptoms, ranging from mild flu-like illness to atypical pneumonia. Approximately 2-5% of all acute Q fever patients are hospitalised.[1,2] Possible factors of importance for hospitalisation are age, sex, smoking behaviour, underlying medical conditions, and pregnancy.[3] Furthermore, exposure to higher doses of *C. burnetii* may increase the severity of disease and thereby lead to hospitalisation.[4-6]

In the Netherlands, Q fever is a notifiable disease to enable outbreak detection and source tracing for effective outbreak control. From 2007 to 2010, the south of the Netherlands experienced large seasonal outbreaks of Q fever with over 4000 notified cases.[7] During those outbreaks about 22% of notified cases were hospitalised, a much larger percentage than reported in the international literature.[8] Some municipalities with higher Q fever incidence and presumably higher infection pressure had lower proportions of hospitalised cases. In addition, diagnostic delay was shown to be inversely related to the number of years that a municipality in the Netherlands had experience with Q fever.[9,10] General practitioners (GPs) in the Netherlands play a pivotal role as gatekeepers for the healthcare system and they take the decision

whether a patient should be referred to a hospital-based medical specialist. We hypothesised that GPs who have more experience with the diagnosis and treatment of Q fever would be less inclined to refer (suspected) acute Q fever patients to hospital, thereby reducing the proportion of hospitalised cases in their geographic area. If this hypothesis holds, this would indicate that early interventions to improve GP knowledge of an emerging infectious disease might reduce hospitalisation rates. In this study, we examined two aspects: the extent of geographic variation in Q fever hospitalisation and its potential association with GP experience with Q fever.

METHODS

We collected information about confirmed and notified cases reported to the public health service 'Hart voor Brabant' during the peak epidemic in the years 2008-2009. 'Hart voor Brabant' is a large public health service region for 1 million citizens, comprising 25 municipalities in the south of the Netherlands and including both urban and rural communities. Most Q fever patients reported during the epidemic resided in this particular region.

The case definition for Q fever is fever, pneumonia or hepatitis in combination with laboratory confirmation by serology or PCR. Laboratories automatically report confirmed cases to the public health service.

On a voluntary basis, further information was obtained from notified cases via telephone interviews performed by public health professionals. Information extracted from the notifications included age, sex, place of residence, date of onset of illness, diagnostic delay (defined as time from the date of specimen collection to date of laboratory diagnosis), possible risk factors for severe disease outcomes (smoking and underlying respiratory diseases), and the name of the GP, which was available when the GP had requested diagnostic tests. Our outcome variable was whether a patient was hospitalised.

We used binomial logistic regression to analyse the association between the risk of hospitalisation and the number of Q fever cases per municipality. We expected the hospitalisation rate to be higher in municipalities with lower numbers of Q fever cases. We adjusted for age, sex, calendar year and underlying respiratory diseases, and municipality was included in the regression model as random effect to account for clustering at municipality level. As the number of Q fever cases is right skewed, the number of Q fever cases was log-transformed. In addition to this, we used linear regression to describe monthly trends of hospitalisation during the study period.

Next, we analysed the association between hospitalisation and the number of previous acute Q fever patients in a particular GP practice. The number of previous acute Q fever patients was used as a proxy for GP experience. We grouped the patients into four arbitrarily chosen categories: one, two, three to seven and eight or more Q fever patients that had visited a GP. We expect the hospitalisation to be lower with increasing GP experience. We used the same binomial logistic regression model as mentioned above, except we replaced the number of Q fever cases by the four GP experience categories.

We also examined the association between diagnostic delay, defined as the duration in days between disease onset and diagnostic confirmation, and GP experience category. This was done by linear regression. Diagnostic delay was log-transformed. To account for clustering at GP level, GP was included in the model as random effect. For reporting, the estimated coefficients were back-transformed.

To evaluate an effect over time on hospitalisation and diagnostic delay, we compared these two outcome measures between Q fever cases diagnosed in 2008 and 2009 using the Wilcoxon test.

To examine whether selection bias could have occurred by only including hospitalised cases for whom the GP name was known, we compared cases with and without GP name known with respect to hospitalisation, age, gender, duration of hospitalisation, underlying respiratory illness and diagnostic delay using a chi-square test.

Statistical analyses were performed using STATA software, version 14.

RESULTS

During 2008-2009, 2044 Q fever patients were reported to the public health service Hart voor Brabant: 705 in 2008 and 1340 in 2009 (*figure 1*). The proportion of cases hospitalised was 17% in 2008 and 14% in 2009. The median duration of hospitalisation was seven days (range: 1-23 days) and did not vary significantly between years (p-value > 0.5).

There was a clear seasonal pattern in total number of acute Q fever cases per month with a peak from April to July. The proportion of cases hospitalised showed an irregular pattern that decreased monthly by 0.7% (95% confidence interval (CI): 0.03-1.3%; p-value = 0.04) (*figure 2*).

The median proportion of cases hospitalised per municipality was 16%. The proportion of cases hospitalised was highly variable between municipalities (range 0-56%, p-value < 0.001) (*table 1*). It was estimated that when the number of Q fever cases of a municipality increases by a factor 10, then the odds of hospitalisation decreases by a factor 0.4 (95% CI: 0.2-0.8).

The name of the GP was registered for 1557 (76%) cases. The proportion of cases hospitalised for whom the GP was

Figure 1. *Number and incidence of notified Q fever patients and proportion of hospitalised patients in 2008-2009, per municipality of the public health service region 'Hart voor Brabant', the Netherlands. A. Incidence of notified Q fever patients per 10,000 citizens per municipality; B. Number of notified Q fever patients and proportion of hospitalised patients per municipality*

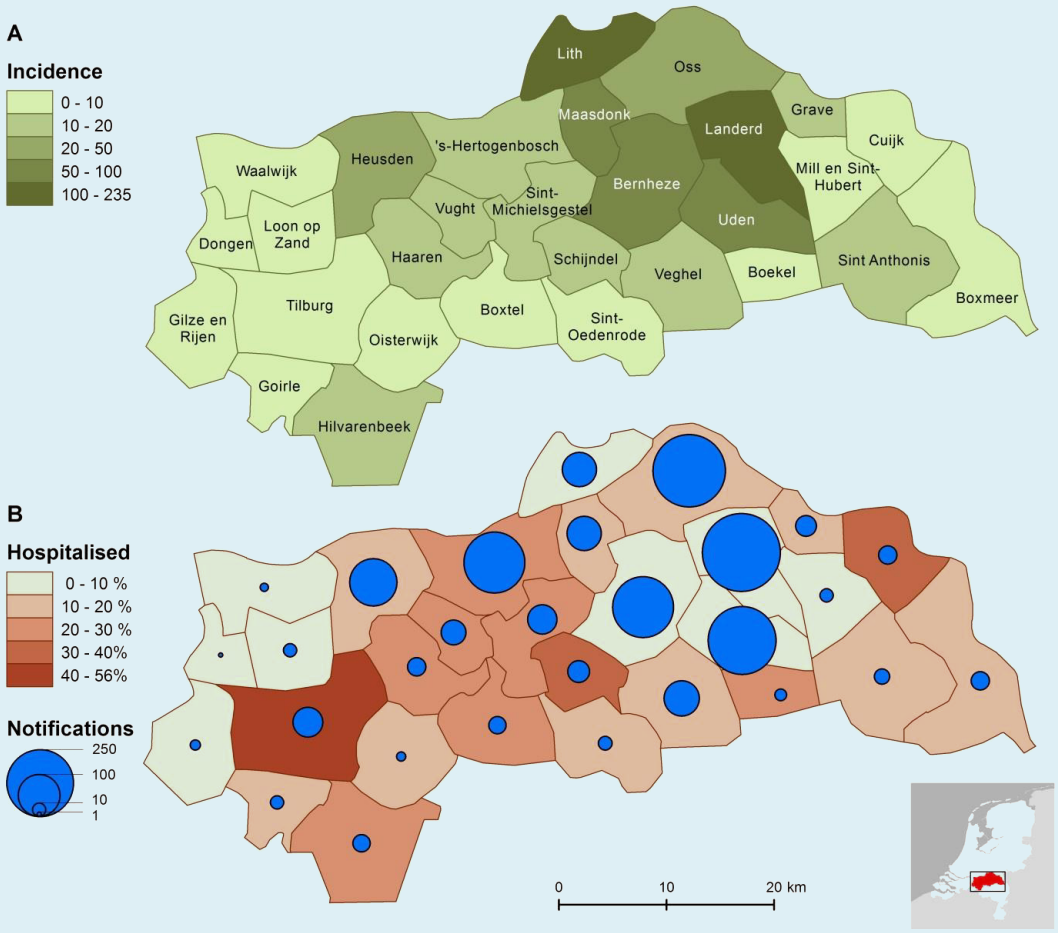

Figure 2. *Proportion of hospitalised Q fever cases in the public health service region 'Hart voor Brabant' per month of onset of symptoms in 2008-2009. The predicted proportion of hospitalised Q fever cases by linear regression is plotted including 95% confidence interval*

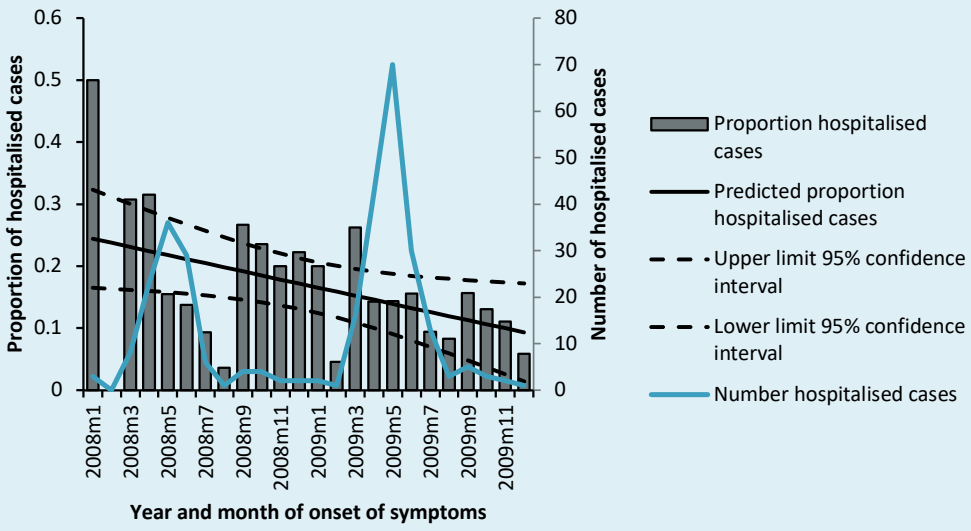

Table 1. *Number of notified Q fever patients and proportion of hospitalised patients by municipality in the public health service region 'Hart voor Brabant', 2008-2009*

Municipality	Population size*	Number of notifications**	Incidence of notifications /10,000	Number of hospitalised cases	Proportion of hospitalised cases in %
Landerd	14,824	348	234.8	17	5
Lith	6675	68	101.9	6	9
Bernheze	29,637	215	72.2	22	10
Uden	40,346	267	66.2	23	9
Maasdonk	11,262	69	61.3	11	16
Oss	77,080	301	39.1	37	12
Heusden	43,014	129	30.0	21	16
Grave	12,745	25	19.6	5	20
Veghel	37,117	72	19.4	13	18
Sint-Michielsgestel	28,193	50	17.7	14	28
's-Hertogenbosch	137,909	214	15.5	59	28
Vught	25,328	36	14.2	9	25
Haaren	13,704	19	13.9	4	21
Schijndel	22,912	28	12.2	9	32
Sint Anthonis	11,801	14	11.9	2	14
Hilvarenbeek	15,041	17	11.3	4	24
Mill en Sint- Hubert	11,020	10	9.1	1	10
Boekel	9701	8	8.2	2	25
Cuijk	24,319	19	7.8	6	32
Boxmeer	28,607	19	6.6	3	16
Sint-Oedenrode	17,439	11	6.3	2	18
Boxtel	30,270	17	5.6	5	29
Goirle	22,503	10	4.4	2	20
Loon op Zand	22,942	10	4.4	0	0
Tilburg	203,468	52	2.6	29	56
Gilze en Rijen	25,799	6	2.3	0	0
Oisterwijk	25,762	5	1.9	1	20
Waalwijk	45,720	4	0.9	0	0
Dongen	25,331	1	0.4	0	0
Total	**1,020,469**	**2044**	**11.3*** **	**307**	**16*** **

* Average population size of years 2008 and 2009.
** included are Q fever cases of whom a 4 digit postal code was known. *** Median incidence and proportion.

known was significantly lower (3% versus 53%; p-value < 0.001) than for cases where the GP was not registered. Of the GPs, 84% had seen more than one Q fever case during this epidemic period (median 6 cases, range 1-65). The risk of hospitalisation declined with increasing experience with Q fever cases seen in a GP practice and was significantly lower for GPs who had attended to eight or more Q fever cases compared with practices that had attended to only one case (odds ratio 0.4 [95% CI: 0.2-0.8]) (*table 2*).

Table 2. *Q fever cases (n = 2045) in the public health service region 'Hart voor Brabant', 2008-2009; diagnostic delay and number of hospitalised Q fever cases per category of general physician experience with Q fever patients*

Number of cases previously seen in a GP practice (in categories)	N	Median diagnostic delay in days, (IQR)	Number of hospitalised cases (%)	Odds ratio of being hospitalised (95% CI)*
1st case	247	31 (17-63)	14 (5.7%)	Reference
2nd case	178	25 (15-36)	10 (5.6%)	0.8 (95% CI 0.4-2.0)
3rd-7th case	468	29 (12-35)	14 (3.0%)	0.5 (95% CI 0.2-1.1)
8th or later case	664	20 (11- 33)	13 (2.0%)	0.4 (95% CI 0.2-0.8)
No GP name known	488	31 (14-64)	257 (53%)	18.5 (95% CI 10.5-32.7)
Total	2,045	24 (12 -42)	308 (15%)	Not applicable

*Binomial logistic regression, adjusted for age, year, season and underlying respiratory disease. IQR = interquartile range.

Table 3. *Characteristics of Q fever patients notified to the public health service region 'Hart voor Brabant', 2008-2009*

	Cases *without* GP's name known (n = 488)	Cases *with* GP's name known (n = 1557)	All cases (n = 2,045)
Median age (IQR)	53 (40-64)	49 (38-58)	49 (38-59)
N males (% male)	307 (63%)	948 (61%)	1255 (61%)
Hospitalisation (%)	257 (53%)	50 (3%)	307 (15%)
Median duration of hospitalisation, days (IQR)	7 (5-10)	5 (4-8)	7 (5-10)
Underlying illness (%)	350 (45%)	765 (48%)	1,115 (47%)
Diagnostic delay, days (IQR)	23 (11-41)	23 (12-37)	23 (12 -37)

IQR = interquartile range. Data are missing for some cases.

Age, sex, duration of hospitalisation, diagnostic delay and proportion of cases with an underlying respiratory illness were not significantly different between cases *with* and *without* a GP name known (*table 3*).

Compared with GPs who had attended to one Q fever case, the mean diagnostic delay was a factor 0.86 (95% CI: 0.73-1.16) lower for GP practices that had attended to two Q fever cases; 0.69 (95% CI: 0.61-0.79) for GP practices that had attended to three to seven Q fever cases and 0.67 (95% CI: 0.59-0.76) for GP practices that had attended to eight or more Q fever cases.

Diagnostic delay decreased significantly from a median of 28 days in 2008 to 18 days in 2009 (p-value < 0.01). The diagnostic delay was slightly lower among cases hospitalised than for non-hospitalised cases (mean 29 versus 33 days, p-value = 0.04).

DISCUSSION

We found small area variations in the proportion of Q fever cases hospitalised in an epidemic region in the south of the Netherlands. In the course of the 2008-2009 epidemic, the proportion of cases hospitalised as well as the diagnostic delay decreased. While a low proportion of hospitalised cases in a municipality cannot be attributed to more experienced GPs in that municipality, the effect of GP experience was measurable at the *individual* practitioner level. Familiarity of a GP with Q fever may prompt early diagnosis and treatment, without the need to refer the patient to hospital.[9,11] It is also likely that high awareness among GPs of Q fever epidemiology leads to more diagnostic testing of suspected cases with relatively mild symptoms, resulting in a lower proportion of patients

hospitalised. Moreover, GPs who suspect Q fever but are unfamiliar with the disease might refer patients earlier to a hospital, even when the symptoms are relatively mild.
After referral of a patient by the GP for hospital evaluation, the final decision whether to admit this patient to hospital is made by a hospital physician. However, in most cases a referral by the GP of a patient with pneumonia will lead to hospital admission and very often the referral follows telephone discussion between the GP and hospital physician.
For the analysis of GP experience, we included patients whose GP was known by the public health service 'Hart voor Brabant'. This leads to exclusion of patients who presented directly at the hospital emergency department and those who were diagnosed by a specialist. Our conclusions about the effect of GP experience on hospitalisation are therefore based upon a presumably clinically milder subset of Q fever cases.
The introduction of the *C. burnetii* PCR in 2008, a more rapid testing technique compared with serology testing, could have contributed to a shorter diagnostic delay.[12] There have been changes in the antibiotics prescribed to Q fever patients, but we assume that there were no further changes in prescribing over the period 2008-2009, which could have had an impact on the hospitalisation rate.[10]
Our findings suggest that the risk of hospitalisation decreases when a GP has seen many Q fever cases. This is our most viable indication that pre-existing knowledge and Q fever experience influence the management of a case and thereby the risk of hospitalisation. The decline in diagnostic delay for more experienced categories of GPs supports the finding that more disease experience has an impact on case management.

We conclude that, for notified Q fever cases, the risk of hospitalisation decreased during the epidemic in the Netherlands. Both the diagnostic delay and the proportion of patients hospitalised were lower for those cases seen by a GP with prior Q fever experience. This suggests that during the Q fever outbreak, increased GP experience led to reduced hospitalisations. Based on these observations, early and targeted information for GPs about the appearance and distribution of an uncommon disease, including diagnostic and therapeutic options, could improve GP knowledge and subsequently decrease the risk of hospitalisation. During the outbreak, the GPs were informed about Q fever by the public health service about four times a year. In addition, countrywide educational sessions became available at a later stage during the outbreak. Anecdotal information suggests that GPs usually read the information when they start to receive patients suspected of having Q fever. We assume, based on our results, there is an opportunity for additional benefit of early targeted information towards GPs to reduce the hospitalisation rate, although the overall effect might be modest.

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DISCLOSURES

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CASE REPORT

Pitfalls in SIADH-diagnosed hyponatraemia: Report of two cases

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ABSTRACT

In the majority of hospitalised patients with hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the primary cause. Before considering SIADH, adrenal, thyroid and pituitary insufficiency should be ruled out. However, the evaluation of these contains potential pitfalls which could lead to incorrect diagnosing of SIADH. Here we present two cases in which a suspected SIADH turned out to be caused by hypopituitarism, emphasising the importance of correctly excluding adrenal, thyroid and pituitary insufficiency.

What was known on this topic?
In the majority of hospitalised patients with hyponatraemia, SIADH is the primary cause. In contrast, hypopituitarism is a much rarer cause of hyponatraemia. Glucocorticoid deficiency in hypopituitarism also leads to inappropriately elevated ADH levels and mimics SIADH. Distinguishing these two clinical conditions can therefore be difficult. As a result, hypopituitarism can easily be misrecognised as a rare cause of hyponatraemia.

What does this add?
We present two cases in which hyponatraemia was caused by hypopituitarism. In both cases, SIADH was the initial diagnosis after apparent exclusion of hypocortisolism and thyroid dysfunction. These cases point out two pitfalls in the evaluation of SIADH. We emphasise the importance of thorough history taking and physical examination as these might raise the suspicion of hypopituitarism. We aim to create greater awareness for underlying endocrinological disorders in any patient with suspected SIADH.

INTRODUCTION

Hyponatraemia, defined as a serum sodium concentration of < 135 mmol/l, is the most frequently encountered electrolyte disorder in clinical practice.[1,2] The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common underlying cause and can be suspected in euvolaemic patients with hyponatraemia, decreased effective osmolality (< 275 mOsm/kg), high urine osmolality (> 100 mOsm/kg of water) and high urine sodium levels (> 40 mmol/l).[2-4] SIADH should only be diagnosed after exclusion of adrenal, thyroid and pituitary insufficiency.[2,4] However, the evaluation of these contains certain pitfalls. To emphasise the importance of correctly excluding adrenal and pituitary insufficiency, we present two cases in which a suspected SIADH was actually caused by hypopituitarism.

CASE REPORT 1

A 74-year-old male patient with no medical history was referred because of hyponatraemia. In the last three months the patient experienced progressive fatigue, weakness, weight loss and recurrent collapses. At the emergency department, a hypotonic hyponatraemia of 128 mmol/l with a urine sodium level of 63 mmol/l and urine osmolality of 671 mOsm/kg were measured. Thyroid-stimulating hormone levels were within the normal range (1.9 mIU/l) after which SIADH was considered the most likely diagnosis. Further evaluation was scheduled at the outpatient clinic.

At presentation, the patient was euvolaemic with a blood pressure of 111/75 mmHg and a pulse rate of 77 bpm. Explicit paleness was present and additional testicular examination revealed an estimated reduced volume of 10 ml. Based on these symptoms and the unexplained hyponatraemia, we suspected adrenal insufficiency. Additional testing revealed hypocortisolism

Table 1. *Overview of the laboratory results on initial and secondary evaluation. The left columns illustrate the initial results on which the diagnosis of SIADH was established whereas the right columns show the additional work-up. Note that different reference values are used per case for cortisol, TSH and IGF-1 due to the use of different laboratory assays*

	Case 1	Case 2	Case 1	Case 2	Reference values	
Sodium	128	99	130	130	135-147 mmol/l	
Potassium	4.0	3.8	4.8	4.9	3.5-5.0 mmol/l	
Serum osmolality	268	209	271	272	280-300 mOsm/kg	
Urine sodium	63	45	96	182	mmol/l	
Urine osmolality	671	525	690	789	300-900 mOsmol/kg	
TSH	1.9	0.56	1.4	0.87	0.30-4.6 mIU/l	
fT4	-		6.0	2.6	10.0-23.0 pmol/l	
ACTH 08:00	-		3.3	5.3	2.2-13.2 pmol/l	
Cortisol 08:00	-		76	140	125-500 nmol/l	
Cortisol 13:49		360			120-620 nmol/l	
Synacthen T = 0	-		-	0.15		
Synacthen T = 30	-		-	0.31		
Synacthen T = 60	-		-	0.36		
LH	-		2.7	1.6	3.0-35 U/l	
FSH	-		4.3	4.4	2.0-18 IU/l	
Prolactin			0.96	13	< 0.37 IU/l	59-619 mU/l
Testosterone	-		< 0.10	-	9.0-28.0 nmol/l	
SHBG	-		105	-	10.0-60.0 nmol/l	
IGF-1	-		8.0	0.8	6.8-23.0	8.4-26 nmol/l

TSH = thyroid-stimulating hormone; fT4 = free thyroxine; ACTH = adrenocorticotropic hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone; SHBG = sex hormone binding globulin; IGF =insulin like growth factor.

with low-normal ACTH levels, hypogonadotropic hypogonadism, central hypothyroidism and mild hyperprolactinaemia (*table 1*). Cranial MRI showed a 15 mm lesion in the sella turcica suggestive of a Rathke's cleft cyst. (*figure 1*). Based on these findings we established the diagnosis of panhypopituitarism due to a Rathke's cleft cyst. After starting replacement therapy with hydrocortisone, levothyroxine and testosterone this patient quickly made a full recovery. Ultimately, the sodium levels normalised to 140 mmol/l. A follow-up MRI scan six months later showed no growth of the Rathke's cleft cyst.

CASE REPORT 2

A 53-year-old Bolivian female patient was admitted to the intensive care unit with severe pneumonia and hypotonic hyponatraemia of 99 mmol/l. She had experienced general weakness for two weeks. Urine sodium was 45 mmol/l and urine osmolality was 525 mOsm/kg. Random cortisol was 360 nmol/l and thyroid-stimulating hormone was 0.56 mIU/l. Therefore, SIADH secondary to pneumonia was diagnosed and the patient was treated with antibiotics, hypertonic saline and water restriction. At discharge, she had fully recovered and her sodium level was 134 mmol/l. One week later she was readmitted with progressive abdominal pain, nausea, diarrhoea and prolonged weakness. On examination she was pale and hypotensive (BP 97/53 mmHg, pulse 72 bpm). Blood tests revealed recurrent hypotonic hyponatraemia of 130 mmol/l with a urine osmolality of 789 mOsm/kg and urine sodium of 182 mmol/l (*table 1*).

Based on the history, hypotension and recurrent hyponatraemia, further testing was performed. A morning cortisol level was 140 nmol/l and the ACTH stimulation test showed an insufficient response. Furthermore, central hypothyroidism and growth hormone deficiency were present (*table 1*). Cranial MRI showed an empty sella

Figure 1. *Cranial MRI of patient A showing a 15 mm lesion in the sella turcica suggestive of a Rathke's cleft cyst. The pituitary stalk is shifted rightwards with a normal positioning of the optic chiasm. The pituitary gland is pressed towards the bottom of the sella turcica*

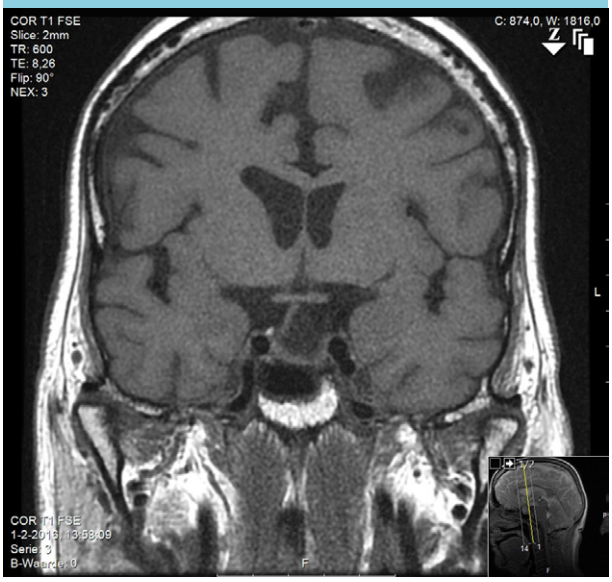
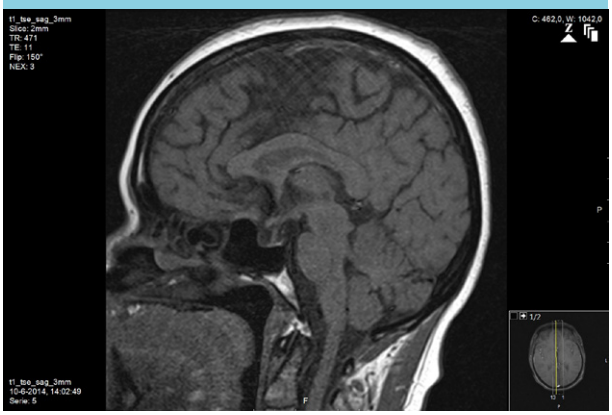


Figure 2. *Sagittal MRI of patient B showing an empty sella. There is a minimal remnant of the posterior pituitary gland visible at the bottom of the sella turcica. The pituitary stalk is slightly shifted rightwards from the midline with normal positioning of the optic chiasm*



(*figure 2*). Additional history taking revealed that her last pregnancy in Bolivia had been complicated by heavy blood loss at delivery for which she received multiple blood transfusions. After this delivery she was unable to provide breastfeeding and she no longer had menstruation. Based on these findings we concluded a panhypopituitarism due to Sheehan's syndrome. The patient quickly recovered after starting replacement therapy with hydrocortisone and levothyroxine.

DISCUSSION

In the majority of hospitalised patients with hyponatraemia, SIADH is the primary cause.[1-3] Underlying reasons for SIADH are diverse but can be subdivided in malignant diseases, pulmonary disorders, central nervous system disorders and the use of certain types of drugs.[2,3] In SIADH, a physiological base (e.g. volume depletion of the extracellular fluid or hypertonicity) for the secretion of ADH is lacking, subsequently leading to inappropriately elevated ADH levels.[3,4]

In contrast, hypopituitarism with secondary adrenal insufficiency is a much rarer cause of hyponatraemia. Space-occupying lesions, trauma or infections in the pituitary gland as well as genetic disorders involved in pituitary development can lead to corticotrophin deficiency.[5,6] As endogenous glucocorticoids suppress both ADH and corticotrophin releasing hormone release in the hypothalamus, glucocorticoid deficiency leads to elevated ADH levels.[7,8] These elevated ADH levels actually mimic SIADH. Hence, distinguishing these two clinical conditions might be difficult, especially in the absence of hypovolaemia or dehydration.[8]

Diederich reviewed 28 cases of severe hyponatraemia due to hypopituitarism with secondary adrenal insufficiency. Scanty/missing axillary or pubic hair (85.7%), nausea or vomiting (75%), a pale, doughy skin (71.4%) and in males a testicular volume of less than 12 ml (71.4%) were the most common clinical signs.[9] Furthermore, anorexia, weight loss, fatigue and lack of energy or stamina are clinical signs of glucocorticoid deficiency often seen in adrenal insufficiency.[5]

The first pitfall described in our cases is the evaluation of thyroid function by measurement of solely TSH. Central hypothyroidism was present in both cases as free thyroxine levels were decreased and TSH was inappropriately normal. Even though hypothyroidism-induced hyponatraemia is rare and might only occur in severe hypothyroidism, the presence of central hypothyroidism could have pointed towards a central endocrinological problem at an earlier stage.[10] Therefore, measuring solely TSH is not sufficient for excluding central endocrinological disorders in suspected SIADH.

Another pitfall is the exclusion of hypocortisolism by randomly measured cortisol levels. As serum cortisol levels are highest in the early morning, a cortisol level of < 100 nmol/l is strongly suggestive of adrenal insufficiency whereas a level of > 500 nmol/l excludes adrenal insufficiency.[5,11] These cut-off values should be interpreted in the clinical context and are variable due to the use of different cortisol assays.[12] Case 2 illustrates that randomly measured cortisol levels are of limited use. As clinical suspicion is high and a basal cortisol level is inconclusive, dynamic testing should be performed. Both

the insulin tolerance test and the short synacthen test have been validated for diagnosing adrenal insufficiency.[5,11,12] However, since the adrenal cortex might still be responsive in the first four weeks after onset of ACTH deficiency, the short synacthen test could be falsely normal.[5,11,12]

CONCLUSION

Hypopituitarism with secondary adrenal insufficiency is a rare cause of hyponatraemia. It can be difficult to distinguish from SIADH, especially in the absence of hypovolaemia or dehydration. In any suspected SIADH, a morning cortisol, TSH and free thyroxine should be included in the initial work-up. If basal morning cortisol levels are inconclusive, dynamic testing of adrenal function should be performed before establishing the diagnosis SIADH.

DISCLOSURES

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CASE REPORT

Congenital methaemoglobinaemia in a 61-year-old patient with normal haemoglobin levels

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ABSTRACT

A 61-year-old Ghanaian woman presented with dizziness and low oxygen saturations whereupon a methaemoglobin level of 24.9% was obtained. Initially it was thought to be caused by an unknown toxin. However, failure to normalise spontaneously and a short recurrence following administration of methylene blue suggested a congenital cause. Subsequently a novel variant in the CYB5R3 gene, coding for Cytochrome b5 reductase, was demonstrated. Absence of polycythaemia prompted additional analysis for a concomitant haemoglobinopathy.

KEYWORDS

b thalassaemia, case report, congenital methaemoglobinaemia, CYB5R3

CASE PRESENTATION

A 61-year-old Ghanaian woman consulted her general practitioner (GP) because of dizziness, headaches, blurry vision and fatigue for three days. Low oxygen saturations of 78-80% upon physical examination made her GP refer her to the emergency department for further analysis.

The patient had a known medical history of well-controlled hypertension and non-insulin-dependent diabetes, for which she had used a thiazide diuretic, gliclazide and metformin for the past years, without recent changes. She did not smoke or use any intoxicating substances. Her symptoms occurred during work at a flower auction, where she had worked for decades. None of her colleagues experienced comparable symptoms. Her job did not involve direct contact with plants, flowers or soil.

The patient had returned from travelling to Ghana three weeks prior to presentation. While there she did not experience any symptoms. She did not use any malaria prophylaxis.

She was non-consanguineous, and had a sister who had died at the age of 30, but no cause was identified at autopsy.

At the emergency department, she did not appear ill or dyspnoeic, with no signs of cyanosis. Measured vital signs are displayed in *table 1*. Further physical examination revealed no abnormalities. Arterial blood gas analysis was performed, the results are shown in *table 1*. Most notable is a significantly elevated methaemoglobin level at 24.9% (normal 1-2%).

The patient was admitted with a provisional diagnosis of acquired methaemoglobinaemia, thought to be caused by an unknown chemical compound possibly contracted during work. She was given 15 litres of oxygen and a single dose of 10 grams oral ascorbic acid (vitamin C). The Ministry of Social Affairs and Employment (Inspectorate SZW) was informed of the incident, as is required by Dutch law concerning (possible) severe workplace-related incidents.

During hospitalisation, the methaemoglobin levels declined in days to 13-14% but no further. Subsequently, methylene blue 1 mg/kg body weight was given intravenously, which resulted in a rapid and significant drop of the methaemoglobin level to 2.9%. The following day the methaemoglobin increased again to 4.8%, suggesting a congenital instead of an acquired cause of methaemoglobinaemia. As the patient was in a good clinical condition with normal oxygen saturation levels without supplemental oxygen, she was discharged.

At the outpatient clinic eight days later the patient reported no symptoms. Arterial blood gas analysis again showed high methaemoglobin levels (15.7%). Because of persistent methaemoglobinaemia in the absence of any apparent

Table 1. *Vital signs and arterial blood gas analysis at presentation and additional haematological screening after admission*

Vital signs		Arterial blood gas analysis	
Blood pressure	186/81 mmHg	**pH**	7.48
Heart rate	79 bpm	**pCO_2**	5.5 kPa (41 mmHg)
Oxygen saturation*	88%	**pO_2**	13.0 kPa (98 mmHg)
Respiratory rate	16 pm	**Base excess**	5.8 mmol/l
Temperature	37.3 °C	**O_2-haemoglobin**	73.7%
***measured by pulse oximetry**		**Methaemoglobin**	24.9%
		Haemoglobin	7.9 mmol/l
Additional haematological screening		**MCV**	78.3 fl
HbA1	72.4%		
HbA2	1.5%		
HbF	26.1%		

triggers, a congenital cause for the methaemoglobinaemia became more plausible. DNA sequence analysis was performed and revealed a novel homozygous variant in the *CYB5R3* gene: NM 000398.6:*c.181C>T, p.(Arg61Cys)*. This variant has not been described in the literature, and has only been found once in the 149,064 alleles of the Genome Aggregation Database. As other pathogenic variants[1-3] are in close proximity to the variant found in our patient, we conclude that this variant is likely pathogenic and thus able to cause congenital methaemoglobinaemia.

With the patient's natural methaemoglobin levels assumed to be around 15%, the sudden increase of methaemoglobin levels and accompanying symptoms as observed at presentation were concluded to be provoked by an unknown substance. Thorough evaluation of her medication, supplements and other products used did not result in a clear causative agent. The Inspectorate SZW could not identify any harmful chemical compounds at her workplace. Reviewing the literature on CYB5R3 deficiency it struck us that it is usually accompanied by a reactive polycythaemia as compensatory mechanism.[4-6] As our patient had normal haemoglobin levels and a low mean corpuscular volume, we performed additional tests demonstrating increased HbF and lowered HbA levels (*table 1*). Genetic analysis revealed a delta-beta thalassaemia (deletion exon 3-9 *HBBP1* gene). Thus, our patient was found to have congenital methaemoglobinaemia caused by a novel homozygous variant, in conjunction with a heterozygous delta-beta-thalassaemia, resulting in normal non-physiological haemoglobin levels.

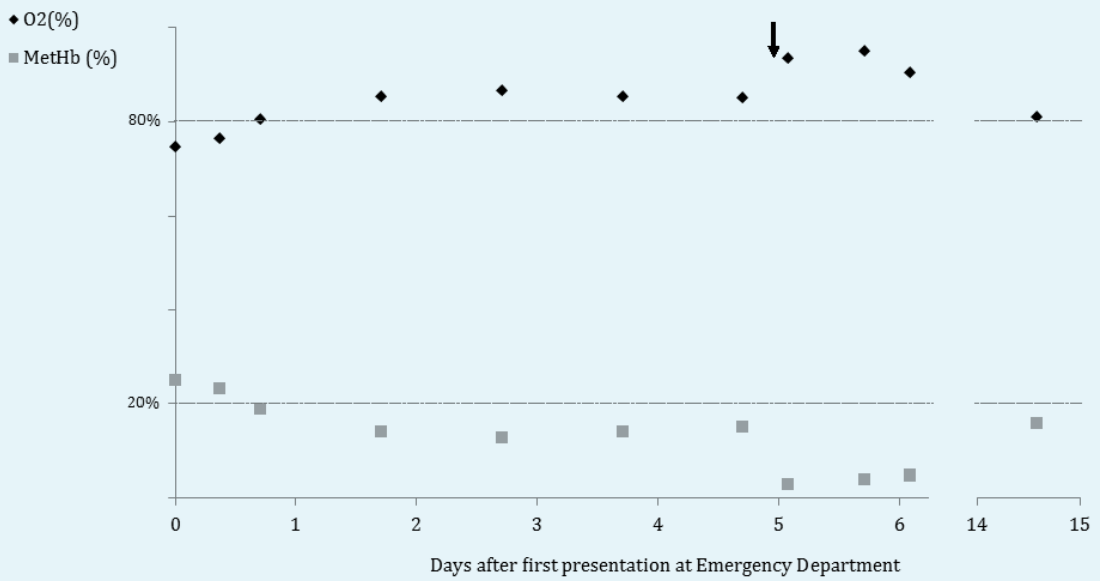
At follow-up, the patient was instructed to abstain from drugs, as some may provoke symptomatic methaemoglobinaemia. She was advised to consult her GP or the emergency department immediately if her symptoms relapsed. Her GP was informed of potential harmful medications and supplements (including sulphonamides, metoclopramide and nitrates) for future reference. An overview of all substances capable of inducing methaemoglobinaemia can be found at www.uptodate.com/contents/clinical-features-diagnosis-and-treatment-of-methemoglobinemia.[7] The combination of these diagnoses has no clinical consequences for the patient. Genetic counselling and testing was offered to her direct family members, including pre-conception counselling for her offspring.

DISCUSSION

Methaemoglobinaemia is a rare condition where blood levels of methaemoglobin are elevated. Methaemoglobin carries ferric (Fe^{3+}) instead of ferrous (Fe^{2+}) iron on haemoglobin molecules, hampering binding of oxygen, causing a cyanotic state.[4,8] Causes of methaemoglobinaemia can be acquired or congenital. Acquired causes are the most prevalent, as various oxidising agents (including certain medications and drugs) are able to increase oxidation activity of ferrous to ferric iron,[8] resulting in an acute methaemoglobinaemia.

Treatment is based on severity of symptoms and methaemoglobin levels. The administration of 1-2 mg/kg body weight methylene blue can adequately reduce methaemoglobin to normal levels.[9] In addition, supplemental high-flow oxygen is effective in elevating plasma oxygen levels, subsequently stimulating conversion of methaemoglobin to haemoglobin.[4] Previously, ascorbic

Figure 1. *Measured levels of O_2-haemoglobin and methaemoglobin in blood gas analysis after presentation at the Emergency Department. Arrow marks IV methylene blue treatment*



acid (vitamin C) was considered an effective treatment,[10] but oral administration does not appear to result in therapeutic plasma concentrations.[11,12]

Most congenital causes of methaemoglobinaemia are based on genetic defects in cytochrome b5 reductase (CYB5R), occurring in almost all ethnic groups. CYB5R deficiency can be expressed in erythrocytes only (type 1), or in all tissues (type 2).[8] Patients with type 1 CYB5R deficiency have persistent pallor or cyanosis, or may remain asymptomatic.[13] In contrast, type 2 CYB5R deficiency results in failure to thrive, severe neurological symptoms and mental retardation.[14,15] Patients with chronically elevated levels of methaemoglobin often have a compensatory polycythaemia.[4-6]

Our patient's first presentation at age 61, together with the apparent acute onset and lack of family history, suggested an acquired cause of her methaemoglobinaemia. While admitted, stabilisation of the methaemoglobin levels to around 14% and absence of possible toxins implied a congenital cause. The observed variant and the absence of symptoms earlier in life, suggest a type 1 CYB5R deficiency in our patient. Heterozygous delta-beta thalassaemia normally leads to low-normal haemoglobin levels or mild anaemia. The combination of type 1 congenital methaemoglobinaemia and carriership of delta-beta thalassaemia resulted in normal haemoglobin levels in our patient.

CONCLUSION

The described combination of two congenital erythrocyte abnormalities has to our knowledge only been reported once, in newborn twins.[16] Our patient did not experience any symptoms related to one or both of the congenital defects until older age. We hypothesise that the combination of both defects with the subsequent adjusted 'normal' haemoglobin levels resulted in these abnormalities going undetected.

DISCLOSURES

This case was presented at the Dutch Acute Medicine Congress in Enschede, the Netherlands, on 10 June 2016. All authors report no potential conflicts of interest.

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PHOTO QUIZ

Asymptomatic facial papules as a marker of genetic syndrome

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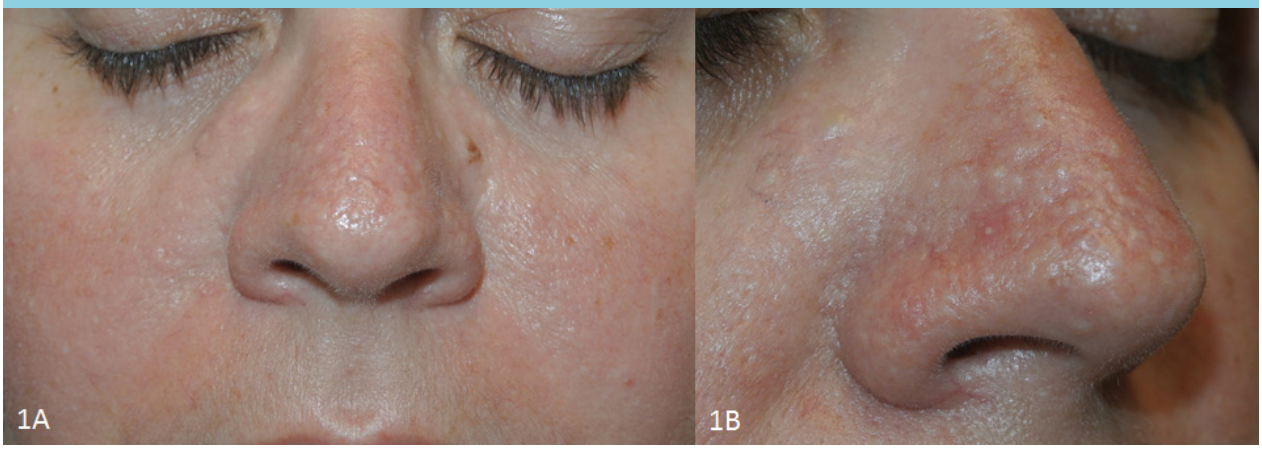
CASE REPORT

A 41-year-old woman presented with multiple asymptomatic flesh-coloured papules distributed over the cheeks and nose. The lesions had been slowly progressive in number during the last eight months. A complete physical examination revealed numerous firm, nontender, dome-shaped lesions on the face, neck and back (*figure 1*). The patient denied any family history of similar dermatological findings or significant medical history. A punch biopsy was performed.

WHAT IS YOUR DIAGNOSIS?

See page 199 for the answer to this photo quiz.

Figure 1. *A. Multiple firm, flesh-coloured papules over the patient's cheeks and nose. B. Clinical detail of small dome-shaped papules*



ANSWER TO PHOTO QUIZ (PAGE 198)

ASYMPTOMATIC FACIAL PAPULES AS A MARKER OF GENETIC SYNDROME

DIAGNOSIS

Fibrofolliculomas. Birt-Hogg-Dubé syndrome (BHD).

Birt-Hogg-Dubé (BHD) is a rare autosomal dominant disorder caused by a germline mutation of the FLCN gene characterised by the presence of benign hair follicle tumours, kidney tumours, pulmonary cysts and recurrent spontaneous pneumothoraces. This syndrome has a great variability in clinical features and patients can present with any combination of manifestations.

The most common systemic finding in BHD is lung cysts, with a 50-fold increased risk of spontaneous pneumothorax. Pneumothoraces in these patients have a high rate of recurrence and pleurodesis is recommended after the first episode.[1,2]

Patients with BHD are at increased risk of developing bilateral, multifocal, renal cell cancers which are the most dangerous complication of this disease. Multifocal and bilateral tumours are seen frequently but most of them tend to be indolent.

Cutaneous findings are common, and sometimes may be the first manifestation of the disease as in the present case. Histology of these lesions most often reveals fibrofolliculomas, but trichodiscomas, perifollicular fibromas, and angiofibromas have also been reported.[3]

There are clinical criteria for the diagnosis of this syndrome. Major criteria are the presence of at least five individual fibrofolliculomas and/or trichodiscomas lesions appearing in adulthood with at least one histologically confirmed and/or presence of a pathogenic PLCN germline mutation. Minor criteria are multiple lung cysts located basally with no other apparent cause (with or without pneumothorax); renal cancer that is either early onset (age < 50 years), multifocal or bilateral or mixed chromophobic/oncocytic histology; or a first-degree relative with BHD syndrome.

To rule out pulmonary or renal manifestations, a baseline chest X-ray or CT scan and abdominal ultrasound must be performed. Currently there are no published guidelines for renal cancer or pulmonary cyst screening in asymptomatic BHD patients or their relatives but recommendations include magnetic resonance or ultrasound for renal cancer screening every 3-5 years from the age of 20 years and a baseline chest X-ray or CT scan and follow-up every 3-5 years to detect asymptomatic pulmonary cysts.[4]

In our patient, gene sequence analysis of FLCN on peripheral blood revealed a heterozygous c.1285 deletion confirming the diagnosis of Birth-Hogg-Dubé syndrome. Screening chest X-ray and abdominal ultrasonography were performed in our patient and both were unremarkable. Follow-up tests have not shown any abnormalities.

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PHOTO QUIZ

It took a torpedo to sink the Lusitania...

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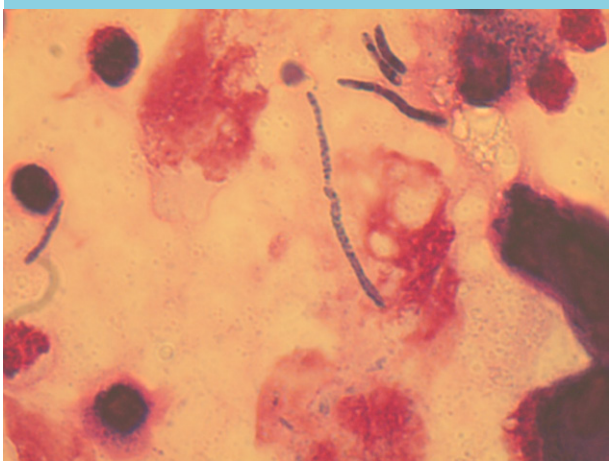
CASE REPORT

A 67-year-old woman was admitted to the hospital with progressive dyspnoea during the last three weeks. Medical history revealed seronegative polyarthritis treated with methotrexate, colon carcinoma and extended hemicolectomy, diabetes mellitus type 2 and hypertension for which she was taking medication. She had been a smoker in the past and drank alcohol daily. Three months prior to admission the polyarthritis worsened, and prednisolone 15 mg daily was added. X-ray of the chest showed diffuse interstitial density, CT scan of the chest showed an atypical image of pronounced density and ground glass opacity. She was treated with penicillin, ciprofloxacin and furosemide, but did not improve. The pulmonologist suspected an immunocompromised state due to long-term use of methotrexate and prednisolone, and feared opportunistic *Pneumocystis jiroveci* pneumonia (PJP). A bronchoalveolar lavage (BAL) was performed and co-trimoxazole and high-dosed prednisolone was started. After the BAL her condition worsened and she was admitted to the intensive care unit (ICU). Physical examination showed a respiratory rate of 35/minute, heart rate of 98/minute, blood pressure of 150/80 mmHg and a tympanic temperature of 37.9°C. Blood gas analysis showed poor oxygenation (pH 7.45, pCO_2 4.2 kPa, pO_2 6.6 kPa, HCO^{3-} 22.2 mmol/l, base excess -1.6 mmol/l, $SatO_2$ 85%) on high-flow nasal cannula oxygen therapy (Optiflow®; FiO_2 = 100%, O_2-flow = 50 litres/minute). She had to be intubated and mechanically ventilated. Laboratory results showed a normal leukocyte and neutrophil count, C-reactive protein 98 mmol/l, and elevated lactic dehydrogenase 433 U/l. The diagnosis PJP unfortunately remained questionable; microscopic examination by silver staining and polymerase chain reaction of the BAL liquid did not show evidence for PJP, however the GIEMSA staining was dubiously positive. But, more surprisingly, fungal hyphae were also noticed (*figure 1*).

Figure 1. *GIEMSA staining of the BAL liquid, showing multiple fungal hyphae*



WHAT IS YOUR DIAGNOSIS?

See page 201 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 200)
IT TOOK A TORPEDO TO SINK THE LUSITANIA…

DIAGNOSIS

Directly after noticing the fungal hyphae we started therapy with voriconazole, suspecting opportunistic infection with *Aspergillus*. But eventually the cultures revealed *Clavispora lusitaniae,* sensitive to voriconazole. Because of persistent doubts about the questionable PJP diagnosis we considered a double infection in an immunocompromised patient, and decided to also continue treatment with co-trimoxazole alongside the voriconazole. Our patient gradually recovered.

Clavispora lusitaniae (until 1996 known as *Candida lusitaniae,* nomenclature by van Uden and do Carmo-Sousa in 1959 because it was first isolated from the alimentary canals of warm-blooded animals in Portugal)[1] is sporadically described as a fungal organism that can cause systemic infection in humans.[2,3] Large studies on the epidemiology of fungal infections show a 1-4% incidence of *Clavispora lusitaniae* among all fungal isolates from blood cultures until 1990; after 1990 the incidence of this pathogen is increasing (2-8%). The reason for this increase is generally thought to be the dramatic increase in use of (adjuvant) chemotherapy for cancer treatment worldwide during that decade.[2] Fungaemia, as primary infection or as co-infection, is mostly seen in immunocompromised patients with underlying malignancies,[2-5] and upon autopsy this yeast is found in the lung, kidney and upper intestinal tract.[4] *Clavispora lusitaniae* is known to develop secondary resistance to amfotericine-B.[2] Although intrinsically susceptible to fluconazole and echinocandins, development of resistance in *Clavispora lusitaniae* isolates during fluconazole and echinocandin treatments was observed.[3,5,6] So, when aiming at this Lusitania, the right 'torpedo' should be chosen: voriconazole.[7]

RMS Lusitania was a British ocean liner, named after the ancient Roman province (Hispania) Lusitania on the west of the Iberian Peninsula, the region that is now southern Portugal. She was launched in 1906 and briefly was the world's largest passenger ship. She made a total of 202 trans-Atlantic crossings, until she was struck by a torpedo launched by a German submarine during World War I. She sank 18 km of the southern coast of Ireland, resulting in the death of 1198 passengers and crew, causing a major diplomatic uproar.[8]

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PHOTO QUIZ

Tongue necrosis

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CASE REPORT

A 74-year-old women with no medical history was admitted to the emergency room with sudden blindness of the left eye. The previous days she had suffered from a painful and swollen neck, jaw claudication and mild temporal headache. Two days before admission she felt a numbness on the left side of her tongue. Physical examination showed dysarthric speech and oedema of the skin and neck. There was a normal consensual response but no direct response with examination of the left pupillary reflex. Blood results revealed elevated ESR (114 mm/h), thrombocytes (750/nl), WBC (17.8 /nl) and CRP (300 mg/l). Ophthalmological examination showed a pale optic disc in the left eye, caused by a central retinal artery occlusion (CRAO). Two days later, the patient suffered from pain when moving her tongue during eating and speaking. We saw progression of the dysarthric speech and a left-sided deviation of the tongue with a blue discoloration, which progressed during the day (*figure 1*). After a couple of days there was a demarcated necrotic aspect on the left side of the tongue with a greyish discoloration (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 203 for the answer to this photo quiz.

Figure 1. *Tongue necrosis, two days after admission to the hospital*

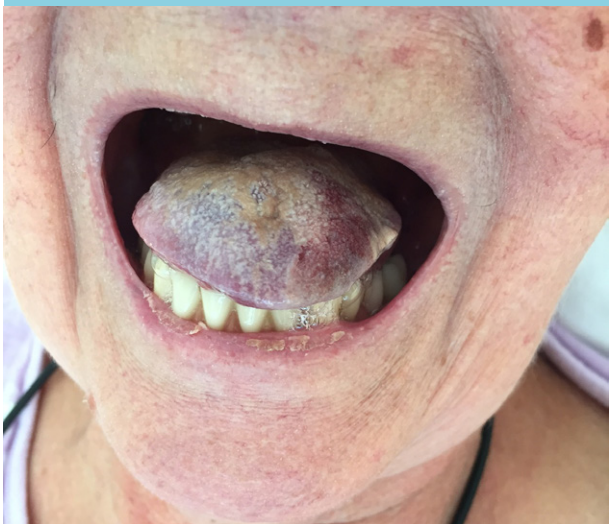
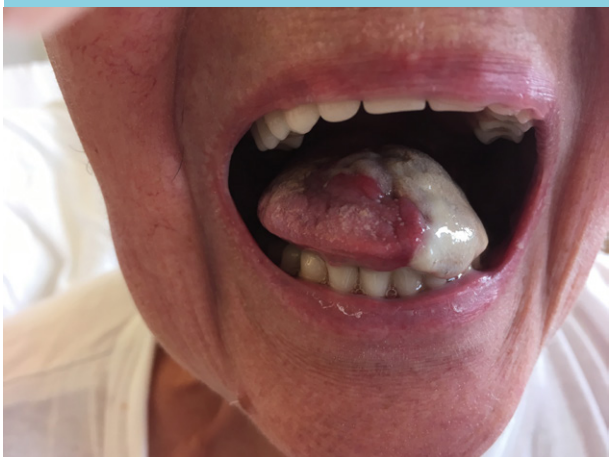


Figure 2. *Tongue necrosis after demarcation*



ANSWER TO PHOTO QUIZ (PAGE 202)

TONGUE NECROSIS

DIAGNOSIS

The patient was suffering from giant cell arteritis which caused tongue necrosis. After admission to the hospital, treatment with methylprednisolone 1000 mg once a day for the next three days was started immediately. Acetylsalicylic acid was started because of the thrombocytosis to prevent other ischaemic complications.

Giant cell arteritis is a chronic and systemic arteritis which involves the large-sized and medium-sized vessels. Almost 60% of all patients with giant cell arteritis report non-specific symptoms such as fever, tiredness and weight loss. Half of patients have dysesthesia of the scalp and jaw claudication. Visual loss occurs in 20% of patients and is caused by anterior ischaemic optic neuropathy or central retinal artery occlusion.[1] Rare symptoms of the head and neck in giant cell arteritis are dysphagia, oedema, tooth pain and necrosis of the lip. Signs of decreased vascularisation of the tongue are pain, burning sensations and tongue claudication.[2] The tongue has a bilateral vascularisation from the lingual artery and a good collateral blood supply. Before tongue necrosis can occur there have to be bilateral problems in the blood supply and for this reason tongue necrosis is a rare complication (≤ 1%) in giant cell arteritis.

Elevated markers of ESR and CRP are common (95%) in patients with giant cell arteritis.[3] Anaemia of chronic disease and raised levels of alkaline phosphatase are frequently present.[4] Ultrasonography of the temporal artery sometimes shows a 'halo sign': a hypoechoic halo around the lumen caused by oedema inside the tunica intima. MRI can show thickening of the vessel wall caused by inflammation. F-FDG PET-scan can show both the extent of inflammation and the severity. A biopsy of the temporal artery remains the gold standard for the diagnosis of giant cell arteritis.[3,4]

In our patient, because of the typical clinical and laboratory manifestations we immediately started treatment with methylprednisolone without a biopsy. During treatment with corticosteroids the inflammatory findings in the blood all decreased and the necrotic part of the tongue spontaneously recovered after two weeks without intervention.

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LETTER

Do not exclude glucarpidase too soon in the context of high-dose methotrexate induced nephrotoxicity

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To the Editor,

We read with interest the article 'Glucarpidase treatment for methotrexate intoxication: a case report and review of literature' by Boelens et al.[1] We would like to address some concerns of the authors.

As the authors correctly state, methotrexate (MTX) induced acute kidney injury (AKI) has the potential to induce a vicious circle in which delayed clearance maintains high systemic MTX levels, causing further kidney damage. Glucarpidase reduces plasma MTX concentrations by > 95% within 15 minutes of administration and is by far superior to extracorporeal techniques in removing MTX effectively from the circulation.

In the recently published 'Consensus guideline for use of glucarpidase in patients with high-dose MTX induced acute kidney injury and delayed methotrexate clearance' by Ramsey et al., a more detailed recommendation for glucarpidase therapy is defined,[2] compared with the original recommendations for use at the time of FDA approval.[3] Both high plasma MTX concentrations at several points after the start of high-dose MTX infusion and the 24-hour serum creatinine concentration are taken into account (a significant elevation (> 1.5) above baseline level). The expert panel concluded that administration of glucarpidase should optimally occur within 48-60 hours from the start of the high-dose MTX infusion, because life-threatening toxicities may not be preventable beyond this point. In the case Boelens et al. describe, the patient received glucarpidase after 85 hours. Clearly, a tighter time schedule necessitates prompt access to glucarpidase.

At the moment of writing, glucarpidase is not registered for use in Europe and hospital pharmacies are not allowed to keep it in stock. This is also the case for several other antidotes. Commissioned by the Ministry of Health (VWS) of the Netherlands, and in cooperation with the Dutch Poisons Information Center (NVIC/UMC Utrecht) a national antidote stock is set up at the National Institute for Public Health and the Environment (RIVM) in 2018. Several rarely used, non-registered and often very expensive antidotes, including glucarpidase, are kept in stock, making these antidotes quickly available in case of medical emergencies. For more information on antidote availability contact the NVIC.

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