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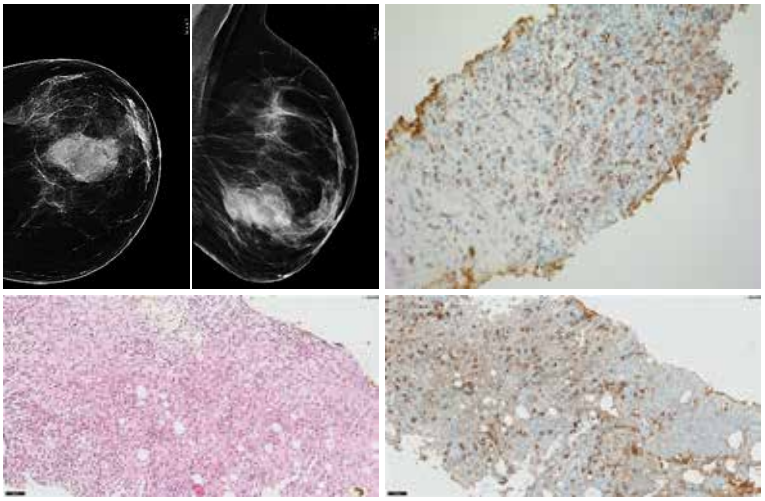
The Journal of Medicine
PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE



A large lump in the left breast: what is your diagnosis?

Ebola

Renal denervation for hypertension

Electrocardiographic abnormalities in patients with hip fracture

Induction therapy in proliferative lupus nephritis

Baclofen intoxication

November 2014, Vol. 72, No. 09, Issn 0300-2977

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ISSN: 0300-2977

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EDITORIAL

Renal denervation revised

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In this issue of the Netherlands Journal of Medicine, a consensus document concerning recommendations for the performance of catheter-assisted renal denervation is provided.[1] This document, issued under the auspices of the Dutch Society of Cardiology, serves as a guide for implementation of renal denervation with care and caution in the Netherlands. Patient safety and creation of transparency are the important achievable aims when performing renal denervation according to the recommendations issued by the Dutch Society of Cardiology. Transparency can be achieved by participation in the independent national registry. In this registry essential clinical data and technical aspects related to the procedure as well as outcome data are documented. The idea behind this database is that we can determine which hypertensive patients will benefit and what kind of immediate and long-term risks are associated with renal denervation.

Patient safety is guaranteed by selecting the right patients to subject to the procedure. The right patient has treatment-resistant hypertension, an eGFR of at least 35 ml/min/1.73 m^2, and renal artery anatomy suitable for intervention. White coat hypertension or a strong white coat effect must be excluded by performing 24-hour ambulatory blood pressure monitoring, as must secondary forms of hypertension requiring other therapeutic approaches. Last but not least, the interventionalist (in most centres a cardiologist) is well experienced in performing this procedure and the multidisciplinary team should include a vascular medicine internist or a nephrologist specialised in hypertension treatment to help to select the right patients and take care of follow-up,

Publication of this document may give the wrong impression that renal denervation is already an accepted and established treatment for patients with resistant hypertension. Although in individual patients renal denervation is sometimes associated with an impressive blood pressure reduction, the recently published Simplicity HTN-3 has shown that the intervention above all has a strong placebo effect.[2] In Simplicity HTN-3, a randomised, controlled trial performed in the United States, 535 hypertensive patients were assigned in a 2:1 ratio to renal denervation or an invasive sham procedure. The mean decrease in systolic office blood pressure at six months was 14.1 mmHg in the renal denervation group as compared with 11.7 mmHg in the sham group (difference of 2.4 mmHg in favour of renal denervation). Reduction in 24-hour systolic ambulatory blood pressure was less than the reduction in office systolic blood pressure, 6.8 and 4.8 mmHg in the renal denervation and sham group, respectively (difference of 2 mmHg in favour of renal denervation). Based on this large controlled study it has to be concluded that, on average, renal denervation is an ineffective treatment. As mentioned, some patients may benefit but at this moment we do not know which ones. Previous results indicate that elderly patients, patients with isolated systolic hypertension and, unexpectedly, patients with impaired renal function are unlikely to respond.[3]

Besides lack of proof of efficacy with regard to blood pressure reduction, evidence of a favourable effect on (cardiovascular) morbidity or mortality, the ultimate goal of treatment of hypertension, is not available for renal denervation and the chance that such information will ever come is small. More importantly, safety issues are also arising. At least 13 cases of *de novo* renal artery stenosis have been reported 3-6 months after renal denervation was performed.[4] Renal artery stenosis is most likely a direct consequence of thermal injury of the renal artery wall induced by the radiofrequency catheter. In addition, a larger than anticipated reduction in eGFR was observed in the Symplicity HTN-1 registry after a follow-up of 36 months, although no difference in change in eGFR between the intervention and sham group was observed in Symplicity HTN-3 after the six-month follow-up period.[5]

Based on the present knowledge we must ask the question whether we should still offer renal denervation to a patient with resistant hypertension. Obviously, different professionals will have different views and considerations. What we at least should do is to inform our patients in an unbiased way. Although renal denervation has already frequently been performed in various European countries and Australia, it is still an experimental treatment, and

after publication of the Simplicity HTN-3 findings, a treatment with minimal efficacy. At least written informed consent from every patient should be required after a full explanation of the technique, including information about the doubtful efficacy and potential immediate and long-term harmful effects.

It remains possible that the disappointing results of Simplicity HTN-3 are in part related to the device used to perform renal nerve ablation. With other devices or techniques a more intensive degree of renal denervation than the maximal 50% denervation obtainable with the Simplicity catheter can probably be achieved, hopefully translating into a larger blood pressure lowering effect.[6] Obviously, before being certain that such a new device really works a new trial with a sham control as done in Simplicity HTN-3 is required. This is also advocated in a recent 'perspective' in the New England Journal of Medicine.[7]

Finally, in the past the proportion of patients with treatment-resistant hypertension suitable for renal denervation has been considerably overestimated. After careful selection, excluding patients with secondary hypertension, patients who are poorly adherent, patients with white coat hypertension or a pronounced white coat effect and patients with an inappropriate anatomy of the renal arteries, only a small fraction of the patients remain suitable for renal denervation.[8] In most of these remaining patients, blood pressure can be controlled by medical treatment when the patient is referred to an expert in the management of hypertension. Thus, although from a scientific point of view it is very disappointing that renal denervation seems to be much less efficacious than initially thought, from a clinical point of view the problem of resistant hypertension is surmountable as in almost all patients with severe hypertension control of the blood pressure can be obtained by lifestyle improvement and optimal pharmacotherapy.

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Ebola virus disease: a review on epidemiology, symptoms, treatment and pathogenesis

M. Goeijenbier[1], J.J.A. van Kampen[1], C.B.E.M. Reusken[1], M.P.G. Koopmans[1,2], E.C.M. van Gorp[1]*

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ABSTRACT

Currently, West Africa is facing the largest outbreak of Ebola virus disease (EVD) in history. The virus causing this outbreak, the Zaire Ebolavirus (EBOV), belongs to the genus *Ebolavirus* which together with the genus *Marburgvirus* forms the family of the *Filoviridae*. EBOV is one of the most virulent pathogens among the viral haemorrhagic fevers, and case fatality rates up to 90% have been reported. Mortality is the result of multi-organ failure and severe bleeding complications. By 18 September 2014, the WHO reported of 5335 cases (confirmed, suspected and probable) with 2622 deaths, resulting in a case fatality rate of around 50%. This review aims to provide an overview of EVD for clinicians, with the emphasis on pathogenesis, clinical manifestations, and treatment options.

KEYWORDS

Ebola virus disease, viral haemorrhagic fever, filovirus, pathogenesis, treatment

INTRODUCTION

On 8 August 2014 the World Health Organisation (WHO) declared the Ebola virus disease (EVD) outbreak in West Africa a Public Health Emergency of International Concern (PHEIC),[1] stressing the need for international attention and collaboration to control the outbreak. At this moment (18 September 2014) a total of 5335 cases with 2622 reported deaths have been notified, in Guinea, Liberia, and Sierra Leone. The imported EVD case in Nigeria that resulted in a relatively small outbreak, and similar imported cases in the USA and Spain which at first appeared to have been well contained, but eventually lead to infection of healthcare workers, show the importance of adequate isolation methods, training of personnel and the adequate use of personal protective equipment (PPE).[2] For the West Africa outbreak the total number of cases is subject to change due to ongoing reclassification, retrospective investigation and the availability of laboratory results. A second, non-related, EVD outbreak has been reported in the Democratic Republic of Congo with currently a total of 62 confirmed and suspected cases.[3,4]

VIROLOGY

The virus causing the outbreak has been characterised as Zaire Ebolavirus (EBOV). EBOV belongs to the genus *Ebolavirus* which together with the genus *Marburgvirus* forms the family of *Filoviridae*. This family belongs to the order of the *Mononegavirales* which further contains members of *Bornaviridae*, *Paramyxoviridae* and *Rhabdoviridae*. *Ebolaviruses* are linear, negative-stranded, RNA viruses with a genome of approximately 19 kilobases. Morphologically, when studied under an electron microscope, the viral particles look like long stretched filaments with some particles tending to curve into an appearance looking like the number 6. At this moment the genus *Ebolavirus* consists of five species: EBOV, Sudan ebolavirus (SUDV), Tai forest ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV). RESTV is considered to be non-pathogenic to humans.[5] The genus is named after the first recognised outbreak that took place in the village of Yambuku, in Zaire (now Democratic Republic of Congo), close to the Ebola river.[6] Since then there have been multiple EVD outbreaks, mostly with EBOV and SUDV. The EBOV responsible for

the current outbreak was introduced into West Africa from Central Africa in the last few decades.[7]

EPIDEMIOLOGY AND WEST AFRICA OUTBREAK

Figure 1 summarises the current area of the West Africa EVD outbreak. This region is known to be endemic for two additional viral haemorrhagic fever viruses (VHF), namely the rodent-borne Lassa fever virus and the mosquito-borne Yellow fever virus.[8,9] Furthermore, a single case of EVD, caused by TAFV, has been reported from this area concerning a female researcher investigating (autopsy) infected chimpanzees.[10] Historically, EVD outbreaks often occurred in small villages close to or located in tropical rainforests. This partly explains why the first outbreaks of EVD, due to EBOV and SUDV, remained restricted to a limited area.[11] No EVD outbreaks were reported between 1979 and 1994, but after 1994 the number of recognised outbreaks increased, leading to the discovery of two new *Ebolavirus* species (BDBV and TAFV).[12] Multiple causes of this increase in EVD outbreaks have been mentioned in the literature, with the most likely being increased bush meat consumption and transportation to previously inaccessible areas.[5,12] EVD is a zoonotic disease and each EVD outbreak in the human population is initiated by a (single) introduction from an animal reservoir. For the current outbreak this introduction occurred in Guinea in December 2013, but it is not known with certainty how the index case became infected.[7] The index case of the unrelated outbreak in the Democratic Republic of Congo had consumed bush meat, which is considered the most likely source of infection.[7,13] Species implicated in introduction of EBOV into the human population are chimpanzee, gorillas, duikers and specific species of fruit bats, all found to be infected with EBOV during targeted studies (*figure 2*). Given the lack of overt disease, bats are considered the most likely reservoir host.[14,15] Once introduced into the population EBOV may spread rapidly, due to the rapid uncontrolled rate of high levels of viraemia and virus shedding in body fluids (saliva, urine, faeces and sweat) by EVD patients.[16] When hygiene and personal protective measures are not adequate, the risk for infection of healthcare workers is considerable, as illustrated in the

Figure 1. *Overview of the area of the current EVD outbreak as per 8 September 2014*

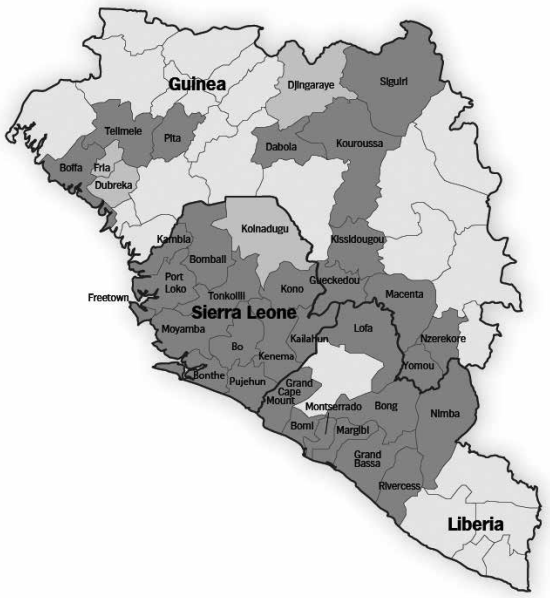
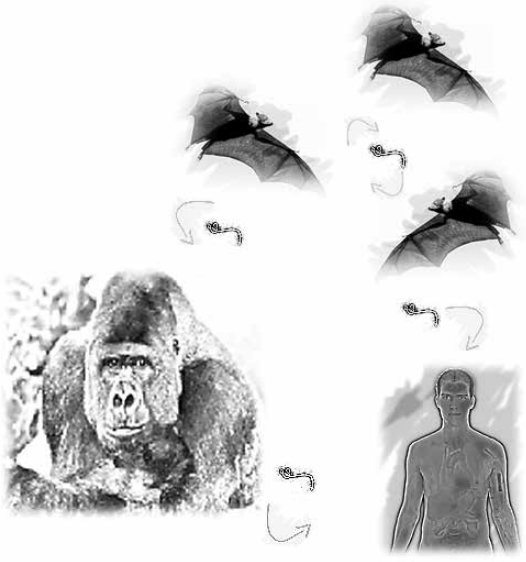


Figure 2. *Transmission of Ebola virus disease (EVD) Ebolaviruses enter the human body via mucosal surfaces, abrasions and injuries in the skin or by direct parental transmission. For each outbreak of EVD a single introduction from the animal kingdom is needed. It is likely that, as for the index case, infection occurs after human contact with primates, e.g. due to hunting or consuming of infected animals, while also other mammals such as antelopes and rodents have been mentioned as potential reservoirs.[61] Another potential cause for human infection was described in 2005 where data from a large study in bats showed three fruit bat species to be a potential reservoir for Ebolaviruses.[14] This was later confirmed by an EVD outbreak that resulted after direct contact with bats.[12,15] Due to the high viral loads seen in the body fluids of EVD patients human to human transmission can easily occur. This transmission seems to take place through body fluid contact and not by airborne transmission (e.g. infective aerosols)*



current outbreak.[17] Furthermore cultural aspects, such as local funeral ceremonies with potential contact with body fluids from patients who have died from EVD, contribute to the magnitude of this outbreak.[18]

CLINICAL MANIFESTATIONS

Symptoms in EVD patients normally occur after an incubation period of 4-10 days, with a range of 2-21 days.[19,20] After a sudden onset of 'flu-like' symptoms (fever, myalgia, chills) and vomiting and diarrhoea, the disease can rapidly evolve into a severe state with a rapid clinical decline. This disease phase is characterised by potential haemorrhagic complications and multiple organ failure.[19,21] EVD patients may present with gastrointestinal symptoms (nausea, stomach ache, vomiting and diarrhoea), neurological symptoms (headache, profound weakness and coma), respiratory symptoms (coughing, dyspnoea and rhinorrhoea), and generalised symptoms related to failure of the cardiovascular system resulting in shock and oedema.[5,20,21] The most commonly described symptoms are fever in combination with anorexia, asthenia and a maculopapular rash between day 5 and 7 after the onset of the disease,[5,20,21] but in the current outbreak the primary clinical presentation is gastrointestinal. Clinical symptoms and chemical laboratory tests confirm multi-organ involvement. Most common haematological changes are leucopenia and lymphopenia, with a specific decreased neutrophil count, and an increase in liver enzymes. With progression of the disease, EVD patients develop thrombocytopenia, lengthening of the pro-thrombin time and activated partial thromboplastin time. The lengthening of the clotting times together with the observed increase in fibrin degradation products suggest a consumptive coagulopathy due to disseminated intravascular coagulation, which contributes to multi-organ failure. Lethal EVD cases generally succumb between day 6 and 16 after the onset of symptoms. Patients die due to shock, haemorrhage and multi-organ failure.[5] If patients recover, clinical improvement arises simultaneously with the development of the antibody response. In lethal cases the antibody response sometimes remains absent.[22,23] Long-term complications of EVD have not been studied extensively, but available literature suggests that patients recovered from EVD could develop long-term symptoms and disorders such as recurrent hepatitis, myelitis, prolonged hair loss, psychosis and uveitis.[5,19,21]

DIAGNOSIS

The diagnosis of acute EVD is made by viral genome detection via RT-PCR. The virus is generally detectable 48 hours after infection in both lethal and non-lethal cases. This means that a negative test result within the first 48 hours after exposure does not rule out EBOV infection. Due to the rapidity of the acute disease, serology does not play a role in diagnosis of acute EVD patients but may be of use in epidemiological and surveillance studies. In general, IgM antibodies can be detected starting from two days after the first symptoms appear and disappear after 30-168 days.[24] IgG response is generally considered to start between day 6 and 18 post onset of illness and remains detectable for years. The antibody profile of the sera from patients with lethal disease as compared with those that survive is markedly distinct. This difference can serve as a prognostic marker for the management of the patient since antibody responses strongly differ between lethal and survivor cases and it has been shown that deceased patients show a much lower or even absent antibody response compared with survivors.[25,26]

PATHOGENESIS AND TRANSMISSION

After infection, development of disease is a complex interplay between virus, host and environment. Different case fatality rates (CFR) have been reported between the four human-pathogenic *Ebolaviruses*. For EBOV the CFR ranges from 50-90% of the EVD cases.[27] For the current outbreak, CFR is estimated to be around 50%,[28] although there is some evidence of improved outcomes with intense symptomatic treatment. There is an indication of differences in the CFR for different EBOV species, but these data are hard to interpret as they rely on reporting, which may be suboptimal.[29] *Ebolaviruses* enter the human body via mucosal surfaces, abrasions and injuries in the skin or by direct parental transmission. Infection through intact skin is considered unlikely, although not excluded. The virus has been successfully isolated from skin (biopsy) and body fluids.[30] Several laboratory associated infections have been reported in the past decades, often after needle accidents or direct contact with infectious materials.[31] The route of transmission seems to affect the disease outcome; in the early EBOV outbreak in 1976, CFR after transmission by injection was 100% versus 80% in contact exposure cases.[5] This has been confirmed in a non-human primate model, showing faster disease progression in animals infected via injection versus those that received an aerosol challenge.[32] Due to the high CFR in EVD and the potential use of EBOV as a biodefense weapon, the pathogenesis of EVD has been relatively well studied during the past 15 years.[33] Most studies have been performed in rodent, guinea pig, primate and *in vitro* models. Since the virus needs to adapt to cause disease in rodent and guinea pig experimental study models, the most relevant data representing human disease come

from non-human primate studies.[34] Upon entry, EBOV have proven to be able to infect numerous cell types. Post mortem studies of patients and experimentally infected animals showed infection of immune cells (macrophages, monocytes and dendritic cells), epithelial and endothelial cells, fibroblasts, hepatocytes and adrenal gland tissue.[35] Replication in infected cells is very efficient resulting in a rapid and high peak viraemia.[35] Furthermore, cell death of infected cells has been hypothesised to play an important role in the signs and symptoms seen in EVD patients, for instance the decreased ability of the immune system to respond to the infection due to necrosis of infected lymphocytes or a decreased production of clotting factor due to the loss of hepatocytes.[5] Hallmark characteristics of EVD, as in any VHF, are the bleeding manifestations although these are infrequently observed in the current outbreak.[36] Studies addressing the mechanism behind these coagulation abnormalities first showed that haemorrhage was most likely not a direct effect of endothelial cell infection, followed by cytolysis.[37] A more likely explanation seems to be an overexpression of tissue factor in monocytes/macrophages resulting in (over)activation of the extrinsic pathway of coagulation followed by a consumptive coagulopathy and eventually a disseminated intravascular coagulation.[38] Furthermore antibody enhancement has been hypothesised to play a role in the later phase of the EVD course.[39] Although data on this theory are still limited, antibody-dependent enhancement seems to enhance infectivity of the virus *in vitro* not only for EBOV but also the closely related *Marburgvirus*.[38,40] A similar disease mechanism has been hypothesised for the development of dengue haemorrhagic fever.[41,42] Interesting data about EVD pathogenesis come from asymptomatic cases and EVD patients who survived infection. A cluster of asymptomatic infections have been described after EBOV infection. Of these 24 contacts, 11 were asymptomatically infected and developed an IgM and IgG response plus a mild viraemia between day 7 (first day of sampling) and day 16.[43] The other 13 patients had high levels of plasma viraemia associated with high levels of pro-inflammatory cytokines. These data suggest that a correlation exists between the height of peak viraemia and levels of pro-inflammatory cytokines contributing to disease severity.

CLINICAL MANAGEMENT AND (EXPERIMENTAL) TREATMENT

The first step is to identify patients with symptoms consistent with the case definition as outlined by the WHO and the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA specially for patients in geographical areas where *Ebolavirus* infections have previously been reported and/or patients in other countries with similar symptoms who have travelled to these countries within the past 21 days. These patients need to be rapidly isolated and the patient contacts identified and appropriate containment and preventive measures instituted. Blood samples need to be immediately obtained and submitted to the nearest clinical laboratory certified to conduct diagnostic evaluation for *Ebolavirus*. Currently, the treatment of EVD includes the administration of 'supportive care' and treatment strategies. EVD patients benefit most from managing the haemodynamics and haemostasis. When started in the early phase of the disease, fluid replacement therapy drastically increases the chance of survival.[44] Ribavirin, the only known antiviral that is effective against certain VHF pathogens such as Lassa fever, is not effective against *Ebolaviruses*.[45,46] Various drugs with a potential effect in EVD are in the experimental phase and have shown beneficial effects against *Ebolaviruses* (mainly EBOV and SUDV) in animal models and have been used in small numbers to treat EVD patients. The WHO declared that, considering the magnitude and severity of the current outbreak, it is ethical to use experimental drugs for treatment and prevention of EVD. *Table 1* shows the most promising experimental compounds with activity against EBOV, and the degree of available information from preclinical and clinical trials published in peer-reviewed journals. ZMapp is a cocktail of monoclonal antibodies and is being used to treat some victims of the current EBOV outbreak. Its role in treatment of EVD still needs to be established since efficacy data in humans have not been published yet. The strongest evidence that ZMapp is indeed effective in EVD comes from experiments in non-human primates in which ZMapp was able to revert advanced EVD when administered up to five days post infection.[47] Unfortunately, there is a limited supply of ZMapp at this moment. Of the non-antibody based antiviral preparations, only the nucleoside analogue favipiravir has been tested extensively in humans. Recently the drug gained approval in Japan for use in humans infected with novel and re-emerging influenza viruses. Besides activity against influenza virus infection, this drug also has documented activity against a wide variety of RNA viruses including *Ebolaviruses*.[48,49] Favipiravir prevented death in mice infected with EBOV when treatment was started six days post infection.[50] These results are promising, but need to be confirmed in a non-human primate model. BCX-4430 is also a nucleoside analogue with broad spectrum activity against RNA viruses and has proven to be effective against the Marburg virus in a non-human primate model and Ebola virus in a mouse model.[51] Finally, TKM-ebola and AVI-6002 are under development for the treatment of EVD and exert their action via gene silencing. Both drugs

Table 1. *Experimental treatments for Ebola viral disease*

Drug	Drug type	Mode of action	*In vitro* data on Ebola	Non-primate animal data on Ebola	Primate data on Ebola	Drug tested in humans	Drug tested in Ebola infected humans	Approval status
Favipiravir (T-705) (Fujifilm Holdings Corp)	Nucleoside analogue – broad spectrum activity against RNA viruses	RNA chain termination and/or lethal mutagenesis	Yes EC_{50} 31-63 mg/l[48] IC_{50} 10 mg/l[50]	Yes 300 mg/kg/d started 1 hour post infection prevented death in 100% of Ebola infected mice[48] 300 mg/kg/d started 6 days post infection prevented death in 100% of Ebola infected mice[50]	Ongoing at USAMRIID [personal communication M. Koopmans and S. Gunther]	Phase-2 completed (influenza) and phase-3 ongoing (influenza)	No	Approved in Japan for novel and re-emerging influenza viruses[49]
TKM-Ebola (Tekmira Pharmaceuticals Corp)	Lipid nanoparticle with siRNA – Ebolavirus specific compound	Gene silencing	Yes	Yes TKM-Ebola started 1 hour post infection resulted in survival of 3/5 guinea pigs (2 deaths unrelated to Ebola)[57]	Yes TKM-Ebola started 30 minutes post infection resulted in survival of 6/8 rhesus monkeys (2 Ebola related deaths)[52]	Phase-1 study partially on hold[9]	No	Not approved
BCX-4430 (BioCryst Pharmaceuticals)	Nucleoside analogue – broad spectrum activity against RNA viruses	RNA chain termination	Yes EC_{50} 3,4 – 11,8 microM	Yes	No, but activity against Marburgvirus in cynomolgus macaques[58]	No	No	Not approved
AVI-6002 (Sarepta Therapeutics)	Phosphorodiamidate morpholino oligomer – Ebolavirus specific compound	Gene silencing	Yes[59]	Yes	Yes AVI-6002 started 30-60 minutes post infection resulted in survival of rhesus monkeys in dose dependent manner (5/8 survived using high dose)[53]	No	No	Not approved
ZMapp (Mapp Biopharmaceuticals)	Cocktail of 3 monoclonal antibodies – Ebolavirus specific compound	Most likely virus neutralisation	Yes	Yes	Yes started 24-48 hours post infection prevented death in cynomolgus macaques and Zmapp is able to revert advanced EVD when administered up to five days post infection[47;60]	Currently being used to treat small number of victims of the current EBOV outbreak	Yes	Not approved

have proven to be effective in mouse and primate models, and some safety and pharmacokinetic data in humans are available for AVI-6002.[52-54] In earlier outbreaks attention was paid to potential treatment of EVD patients with blood transfusion from EVD survivors. For instance, in the EVD outbreak in Kikwit (Democratic Republic of Congo) in 1995, patients receiving convalescent serum from EVD survivors showed a much lower CFR.[55] However these results were based on a small number of patients with a potential treatment bias. Furthermore, this passive immunotherapy did not seem to be effective in a non-human primate model.[56] Due to the potential for antibodies to enhance viral infections via antibody-enhancement mechanisms,[59] a note of caution is in order

for the use of passive immunotherapeutic strategies. However, there have been studies using such passive immunotherapeutic protocols, especially with monoclonal antibody treatment, which have been shown to be quite effective in non-human primate models of *Ebolavirus* infection and need to be considered.

CONCLUSION

Rapid and wide geographic spread of the current EBOV outbreak are reasons for increased alertness of clinicians dealing with returning travellers from the outbreak areas. Due to the initial non-specific presentation of EVD, the combination of fever (and/or EVD symptoms such as nausea, flu-like illness, headache, diarrhoea, myalgia, conjunctival effusion and redness of the oral and pharyngeal mucosa) in combination with high-risk exposure (contact with EVD patient or body fluids, wild animals, attendance of a funeral, visit to a local healthcare facility or preparing and/or consuming bush meat) is enough to proceed with isolation and management protocols in patients who visited endemic areas in the last 21 days. Currently treatment strategies rely solely on the early start of supportive care, where aggressive fluid replacement therapy is proven to drastically improve the survival rates. Specific antiviral EVD treatment strategies are still in the experimental phase. The current EVD outbreak stresses the already weak healthcare and public health systems in the affected countries, but also triggers increased awareness in countries at risk for EVD import cases. Given the ongoing outbreak, countries and clinical centres should be aware of the potential for admission of an EBOV infected person.

DISCLOSURE

The authors declare no conflicts of interest in the preparation of this manuscript.

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SPECIAL REPORT

Renal denervation for the treatment of hypertension: the Dutch consensus

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ABSTRACT

Since 2010, renal denervation (RDN) is being performed in the Netherlands. To make sure RDN is implemented with care and caution in the Netherlands, a multidisciplinary Working Group has been set up by the Dutch Society of Cardiology (NVVC). The main aim of this Working Group was to establish a consensus document that can be used as a guide for implementation of RDN in the Netherlands. This consensus document was prepared in consultation with the Dutch Association of Internal Medicine (NIV) and the Dutch Society of Radiology (NVVR).

KEYWORDS

Renal denervation

INTRODUCTION

Since 2010, renal denervation (RDN) is being performed in the Netherlands. RDN is a percutaneous catheter therapy for the treatment of resistant hypertension and is based on a promising concept. The first studies that investigated the efficacy of RDN showed impressive blood pressure reductions.[1,2] However, more recently the sham-controlled Symplicity HTN-3 trial demonstrated a less pronounced reduction of blood pressure and a relevant placebo effect.[3] To implement RDN with care and caution in the Netherlands, a multidisciplinary working group has been set up by the Dutch Society of Cardiology (NVVC). The overall consensus is that RDN seems a promising therapy to lower BP.

At present, RDN is being used in two groups of patients:

- In patients with resistant hypertension.
- In patients fulfilling the same blood pressure criteria, but without optimal pharmacological treatment due to recorded intolerance for antihypertensive drugs. These patients often pose dilemmas to the treating physician.

Resistant hypertension is defined as a blood pressure that remains above goal despite the concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.[4] Patients whose blood pressure is controlled with four or more antihypertensive drugs are also considered to have resistant hypertension.[4] The main aim of this Working Group was to establish a consensus document that can be used as a guide for implementation of RDN in the Netherlands. This consensus document was prepared in consultation with the Dutch Association of Internal Medicine (NIV) and the Dutch Society of Radiology (NVVR). The principle is that a patient is being treated with a blocker of the renin-angiotensin system (RAS), a thiazide diuretic and a calcium antagonist in optimal dosages. In addition, it is preferable to add an aldosterone antagonist to the drug regimen. Patients should be screened first before they are treated by RDN. Screening of patients may be considered when they have an office systolic blood pressure of ≥ 160 mmHg. Subsequently a 24-hour ambulatory blood pressure

measurement should be performed while the patient is using antihypertensive drugs to exclude white coat hypertension.[5] Since 1 January 2013, there is a conditional reimbursement for RDN in the Netherlands.

Principles of the consensus document

In the future, RDN may have an important place in the treatment of patients with resistant hypertension. The indication of RDN might be expanded to milder forms of hypertension. However, further research is needed for such indications. The hospital in which RDN is performed must meet certain criteria regarding infrastructure and organisation.

When writing the present consensus document on RDN, two elements played an important role:

- In the first place: the safety of the patient.
- In second place: transparency. This transparency refers to:
  - Participation in the national registry. In this national database essential clinical data and technical aspects of the procedure are prospectively documented.
  - Reporting of clinical results.

Based on the above, the Working Group states that it is highly preferred that each patient who undergoes RDN should be treated in the context of a study or trial. At least, the patient should be included into the national registry. This is an online database operated by the Julius Center for Health Sciences and Primary Care. The Julius Center is an independent centre and will only perform analysis on the registry after written approval of the participating centres.

Standards of quality

A hospital that wants to qualify for RDN should comply with all of the following criteria to meet the optimal conditions for patient safety:

- The department of radiology or cardiology of the hospital has a catheterisation room with access to up-to-date X-ray equipment with support by experienced technicians and nurses. There is also the appropriate infrastructure to deal with any complications.
- The department of radiology or cardiology features:
  A subdivision of interventional radiology in which at least one specially designated radiologist (interventional radiologist) performs catheter-based treatments of the greater vessels on a weekly basis (> 50 annually):
  Be it a subdivision of intervention cardiology which, according to the criteria of the NVVC and in accordance with the Act on Exceptional Medical Operations (WBMV), is authorised to perform percutaneous interventions;
  Or a subdivision of clinical electrophysiology that, according to the criteria of the NVVC and in accordance with the WBMV, is authorised to perform electrophysiology catheter ablations.
- The hospital has a department of general surgery with a (sub) section on vascular surgery.
- The hospital has a vascular medicine specialist and / or a nephrologist specialised in hypertension, where patients can go for the exclusion of secondary causes of hypertension.
- Any patient who qualifies for RDN is discussed beforehand in a multidisciplinary team. This team is responsible for the exclusion of secondary causes of hypertension.
- Ambulatory blood pressure measurements, outpatient blood pressure measurements on the left and right arm, laboratory testing (serum and urine), and detailed imaging should be first performed to exclude secondary causes of hypertension. Preferably, the laboratory measurements are performed during a drug-free period to prevent the influence of the drugs on these measurements. The following measurements should be performed:
  Serum tests: Sodium, potassium, creatinine, haemoglobin, fasting glucose, fasting lipid spectrum, thyroid-stimulating hormone, plasma renin activity or plasma renin concentration and aldosterone according to the guidelines of the Endocrine Society.[6]
  24-hour urine collection: Sodium, creatinine, protein and albumin. Determination of metanephrines may be considered if there is a clinical suspicion of pheochromocytoma.
  When Cushing's disease or Cushing's syndrome is suspected, saliva cortisol or 24-hour urinary cortisol can be determined.
  When it is deemed medically unsafe to temporarily stop antihypertensive drugs, no reliable judgment can be made upon a possible primary hyperaldosteronism. In such cases the physician can consider to take the measurements under 'rescue-drugs' (diltiazem and/or doxazosin). Measurement of the aldosterone-renin ratio while using antihypertensive drugs is generally useless to diagnose primary hyperaldosteronism. A computed tomography (CT) scan may show incidentalomas, which can subsequently lead to extra diagnostics. When there is doubt about the diagnosis of primary hyperaldosteronism, a sodium-challenge test should be performed. Except for incidentalomas, the multidisciplinary team should realise that micro-adenomas can be easily missed at CT or magnetic resonance imaging (MRI).
- Secondary causes of hypertension that should first be excluded are:
  - Primary hyperaldosteronism
  - Cushing's syndrome
  - Coarctation of the aorta
  - Pheochromocytoma
  - Excessive liquorice intake
  - Thyroid disorders

The reason for exclusion is that these conditions require a distinctly different treatment. In *Appendix A* advice is given about the implementation of the various measurements.

- In the anamnesis the patient should be asked about medication compliance. In *Appendix B* the Morisky questionnaire is provided. This is a validated questionnaire that can be used to inform about medication compliance. When in doubt about compliance, this must be analysed. Documenting the impact of supervised intake of antihypertensive drugs on the blood pressure is hereby recommended. Furthermore one can determine the ACE activity in a patient who is on an ACE inhibitor.
- Lifestyle advice should be given to and implemented by the hypertensive patients before RDN is considered. This advice should include a reduced salt intake.
- To evaluate the anatomy of the renal arteries non-invasive imaging should be carried out before RDN is performed. Preferably CT angiography (CTA) or MR angiography (MRA) are used as non-invasive imaging modalities. A conventional angiography may also be considered. This (non-invasive) imaging will provide information to evaluate whether the anatomy of the patient is suitable for RDN. The following criteria should be met:
  - The renal artery has a diameter of ≥ 4 mm and a length of ≥ 20 mm.
  - No significant haemodynamic or anatomic renal artery stenosis is present.
  - One main renal artery is present on both sides with a diameter of ≥ 4 mm.

  Immediately prior to RDN a conventional angiography should be performed.
- A multidisciplinary team should be established, consisting of the physician performing RDN and a supporting specialist who has excluded secondary forms of hypertension. Each patient must be discussed in this team prior to screening for true hypertension and after the screening to reach consensus about the indication for RDN. Both eligible and non-eligible patients should be registered in a database.
- Absolute contraindications for RDN are:
  - GFR < 30 ml/min/1.73 m^2
  - A haemodynamicaly significant renal artery stenosis (> 50%)
  - Fibromuscular dysplasia of the renal artery
  - A secondary cause of hypertension
  - Nephrectomy or a mono-kidney (considering the present lack of data on the effects of the RDN procedure in these patient groups)
  - Pregnancy (considering the radiation during the procedure)
  - Incompliance for antihypertensive drug treatment
- Besides absolute contraindications, there are also relative contraindications to RDN. When one of the following is present, the physician performing RDN should be cautious about potential complications and precautions must be taken.
  - Contrast allergy
  - Atherosclerosis
  - A non-significant renal artery stenosis (< 50%)
  - Severe peripheral artery disease
  - Aortic bifurcation prosthesis
  - Coagulation disorders
- For the prevention of thrombus formation we recommend to prescribe antithrombotic therapy to the patient. Preferably aspirin 100 mg once daily is given starting three days prior to the procedure up to 30 days after the procedure.
- The team that performs RDN, consisting of the interventional cardiologist, interventional radiologist, or electrophysiologist and all relevant supporting disciplines, should have been extensively trained in the procedure. Training offered by the manufacturer, training in the skills lab or training in another centre can all be used for this purpose.
- The physician performing RDN carries out at least 20 RDN procedures annually. This number is achieved through a system of ingrowth, whereby the minimum of 20 procedures annually should be established after two years.
- The physician performing RDN has successfully completed a fellowship in interventional radiology, interventional cardiology, or clinical electrophysiology.
- In the hospital performing RDN, a protocol is present in which all steps of RDN are documented. This protocol includes the screening investigations in the outpatient clinic, the clinical aspects of the procedure itself, and the follow-up.
- The hospital has an electronic database in which relevant data on patient, procedure and complications can be registered.
- The hospital is participating in the national registration on renal denervation (operated by the Julius Center for Health Sciences and Primary Care). In this registry key demographic, clinical, and technical data and outcomes are recorded. The hospital cooperates with (ad hoc) audits and quality.
- The Working Group on RDN will report annually to the NVVC, the NIV, and the NVVR about national results of RDN procedures in the Netherlands.
- Every year, there should be a follow-up of patients who have undergone RDN. During this follow-up the 24-hour blood pressure, the number of antihypertensive drugs, and the renal function should be monitored. During the follow-up one year after treatment, we recommend to perform non-invasive

imaging of the renal arteries (the same modality as used prior to RDN). During follow-up, antihypertensive drugs should be continued. When adjustment (reduction or increase) of antihypertensive drugs is indicated, in the opinion of the treating physician, this should be done. We advise to follow the patients every six months during the first three years, and thereafter annually for up to five years after RDN. The national database will send reminders to the treating physician if the online follow-up questionnaire has not been completed. Appendix C provides an example for the follow-up.

DISCLOSURES

P.J. Blankestijn: Research funding received from Medtronic, speakers and advisory fees from Medtronic and St Jude Medical; M. Voskuil: Procter/consultant Medtronic. The other authors declare no conflicts of interest.

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APPENDIX A.

Advice from the Working Group regarding the performance of various assessments to exclude secondary hypertension.

Imaging of the renal arteries
By performing imaging of the renal arteries, renal artery stenosis can be excluded. Preferably, imaging is performed by MRA / CTA or conventional angiography.

Temporary stop of antihypertensive drugs
In order to obtain reliable results from the laboratory assessment it is strongly recommended that patients stop taking their antihypertensive drugs for at least two weeks prior to the investigations. Most antihypertensive drugs may simply be stopped at once, with the exception of beta blockers and centrally acting antihypertensives (methyldopa, clonidine, and moxonidine), which should be tapered. Stopping or tapering can be done as follows:
Four weeks prior to the investigations:
Stop: diuretics (including aldosterone antagonists) and aliskiren
Taper in two weeks, starting four weeks prior to the investigations: beta blockers and centrally acting antihypertensives according to the following scheme:

Day 1	100%	Day 6	0%	Day 11	25%
Day 2	50%	Day 7	50%	Day 12	0%
Day 3	50%	Day 8	0%	Day 13	25%
Day 4	50%	Day 9	25%	Day 14	0%
Day 5	50%	Day 10	0%		

Using this scheme, the beta blockers and centrally acting antihypertensives may be stopped two weeks prior to the investigations.
Two weeks prior to the investigations:
Stop: ACE inhibitors, calcium antagonists, alpha blockers, direct vasodilators. Also, no NSAIDs should be used in this period.

Rescue medication
If it is deemed unsafe by the treating physician to temporarily stop the antihypertensive treatment, rescue medication can be given. Examples of rescue medication are diltiazem retard (200 mg or 300 mg once daily) or doxazosin retard (4 mg or 8 mg once daily). When a patient experiences side effects from the medication stop, these rescue drugs may also be prescribed.
Next to the stopping and/or tapering of antihypertensive drugs, patients should be told that

in the 3-4 days prior to the examinations it is very important to maintain a constant daily salt intake. In daily practice this means that especially (extremely) salty meals (ready-to-eat meals, pizza, soup) should be avoided.

Interim control of potassium
In order to prevent a possible hypokalaemia from affecting the aldosterone-renin test, the potassium is determined at the end of the first medication-free interval. Hypokalaemia may lead to a false-negative outcome of the test. In the case of hypokalaemia, temporary potassium supplements are advised.

Saliva cortisol
The patient is given a salivette and instructions to collect saliva cortisol. In the second medication-free week the patient is instructed to take saliva at home at 23.00 hours. The saliva sample should be stored in the fridge and sent to the laboratory.

Blood sampling
The following measurements should be performed: Sodium, potassium, creatinine, urea, glucose, cholesterol, HDL, LDL, triglycerides. The blood can be drawn from the infusion after a dummy tube is taken to rinse off the NaCl from the infusion. After withdrawing blood the infusion should be injected with 3 ml of NaCl 0.9% to prevent clotting.
Measurement of glucose, cholesterol, HDL, LDL, and triglycerides should be performed under fasting conditions.

Aldosterone-renin ratio
The purpose of the aldosterone-renin test is to determine hyperaldosteronism. This test should be performed under the conditions prescribed in the guidelines from the Endocrine Society.[6]

24-hour urine collection
Patients are given a container to collect urine for 24 hours. From this 24-hour urine the following measurements can be done: sodium, potassium, creatinine, protein, albumin and metanephrines (the last when indicated). When indicated catecholamines or cortisol can also be determined in the 24-hour urine or in a urine sample.

APPENDIX B.

The Morisky 8-Item Medication Adherence Scale

1. Do you sometimes forget to take your high blood pressure pills?
2. Over the past two weeks, were there any days when you did not take your high blood pressure medicine?
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
4. When you travel or leave home, do you sometimes forget to bring along your medications?
5. Did you take your high blood pressure medicine yesterday?
6. When you feel your blood pressure is under control, do you sometimes stop taking your medicine?
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?
8. How often do you have difficulty remembering to take all your blood pressure medication?

Alpha reliability = 0.83
Morisky *et al*. J Clin Hypertens. 2008;10:348-54

APPENDIX C. OUTPATIENT FOLLOW-UP AFTER RENAL DENERVATION

3-6 weeks after the procedure
Control of the groin
Outpatient blood pressure measurement in both arms
Laboratory investigations (renal function, electrolytes, haemoglobin)

3 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.

6 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements may be considered

9 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.

12 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)
Non-invasive imaging of the renal arteries may be considered

18 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements

24 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)

36 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)

48 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements

60 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Electrocardiographic abnormalities in patients admitted for hip fracture

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ABSTRACT

Background: Several risk factors for falls and hip fractures have been recognised, but controversy still exists regarding the importance of rhythm and conduction abnormalities as potentially modifiable risk factors for recurrent falls. The aim of this study was to determine the prevalence of clinically relevant ECG abnormalities in patients with a hip fracture versus controls.

Methods: The study was designed as a case-control study within consecutive hip surgery patients in an academic hospital. Cases: patients with traumatic hip fractures. Controls: patients undergoing planned hip surgery (non-traumatic). Cases and controls were 1:1 matched for age and gender. Inclusion criteria: age ≥ 50 years. Exclusion criteria: high-energy trauma, pathological and/or previous hip fracture. ECGs were scored using predefined categories. Multivariate logistic regression was performed to calculate odds ratios (OR) and to correct for confounders.

Results: We included 888 patients (444 cases). Mean age was 70.9 years (SD 9.3), 70% were female. After correction for potential confounders we found the following associations between clinically relevant ECG abnormalities and hip fractures: atrial fibrillation OR 2.7 (95% CI 1.2-6.1), abnormal QTc prolongation OR 3.9 (2.2-6.8), sinus tachycardia OR 5.0 (2.1-11.8) and sinus bradycardia OR 0.3 (0.1-0.5). Univariately, several markers for decreased cardiac function were also associated with hip fractures.

Conclusions: Hip fracture patients are at higher risk for ECG abnormalities than matched patients undergoing hip surgery for other indications. To potentially reduce the risk of future (injurious) falls, increased awareness of these ECG abnormalities is warranted to assess the need for further cardiovascular fall risk assessment.

KEYWORDS

Atrial fibrillation, ECG, falls, hip fracture, QTc prolongation

INTRODUCTION

Hip fractures in older persons form a substantial and growing healthcare burden.[1] Hip fractures lead to an excess one-year mortality rate of 25%, and 50% of survivors of hip fractures suffer from a significant decline in quality of life.[1,2] Prevention of hip fractures is therefore of great importance. Since > 90% of hip fractures are due to a fall, a multifactorial intervention is warranted when assessing treatable risk factors to prevent a (recurrent) injurious fall.[3] Several risk factors for falls and hip fractures have been recognised, including muscle weakness, history of falls and visual deficits.[3,4] However, controversy still exists regarding the importance of cardiac arrhythmias as a potentially modifiable risk factor for falls.[3] Only a few studies have investigated the association between cardiac rhythm and conduction abnormalities and hip fractures.[5-8] Although these studies suggest a potential association between cardiac arrhythmias and hip fractures, results were inconclusive due to small sample sizes and lack of adequate comparison groups.

If we could determine whether cardiac arrhythmias, conduction abnormalities and other electrocardiographic (ECG) abnormalities are indeed associated with hip fractures, this may provide us with new evidence on (potentially treatable) risk factors for injurious falls. In the current study we therefore investigated whether ECG abnormalities were more prevalent in hip fracture patients compared with planned hip surgery patients. We

hypothesised that hip fracture patients have more clinically relevant ECG abnormalities, potentially explaining fall incidents, than study controls.

METHODS

Population

The study was conducted according to the principles expressed in the Declaration of Helsinki. The medical ethics committee of the Academic Medical Center (Amsterdam) approved this study and waived the necessity for informed consent because of the observational design. The study was designed as a case-control study within consecutive patients undergoing hip surgery. All patients admitted for either planned or emergency hip surgery from January 1996 to May 2011 in a tertiary university teaching hospital were screened for eligibility. Cases were defined as patients with traumatic hip fracture who underwent subsequent proximal femur fracture surgery. Controls were defined as patients who underwent elective hip surgery for non-traumatic reasons, mainly total hip replacement. Inclusion criteria were age ≥ 50 years and preoperative ECG present in the hospital records. Exclusion criteria were previous hip fracture, high energy trauma and pathological fracture. Patients were individually matched 1:1 for age and gender. Age was categorised in groups of five years to increase likelihood of matching.

Baseline characteristics

For data collection, all electronic and paper medical records were retrieved. Admission duration was recorded in days. All functional limitations and comorbid diagnoses (noted in the medical records and/or referral letters) were recorded. Functional limitations included a previous fall (mention of a fall in the past medical history), use of a mobility aid (walker, cane or wheelchair), visual impairment or deafness. Further comorbid diagnoses included coronary artery disease (previous medical history of angina pectoris, myocardial infarction/percutaneous transluminal coronary angioplasty and/or coronary artery bypass graft surgery), hypertension, heart failure, heart valve disorder, cerebrovascular accident, atrial fibrillation, pacemaker or internal cardiac defibrillator, parkinsonism, cognitive impairment, alcohol abuse, diabetes mellitus, chronic obstructive pulmonary disease, hemiplegia/paraplegia and depression.[10] As an overall measure of comorbidity, the Charlson Comorbidity Index (CCI) was computed.[9] Among other conditions, the CCI includes myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, liver disease, renal disease and chronic pulmonary disease.

Drugs were listed and grouped according to the Anatomical Therapeutic Chemical (ATC) classification system. Medication categories adjusted for in our analysis were psychotropic medications: psycholeptics (N05*) and psychoanaleptics (including antidepressants) (N06*), and cardiovascular medications: cardiac therapy (cardiac glycosides, class I and III antiarrhythmics, cardiac stimulants, vasodilators and other cardiac preparations) (C01*), antihypertensives (C02*), diuretics (C03*), peripheral vasodilators (C04*), beta blockers (C07*), calcium channel blockers (C08*), agents acting on the renin-angiotensin system (C09*), alpha-adrenoreceptor antagonist urologicals (G04CA) and beta blocker antiglaucoma preparations (S01ED). QTc-prolonging drugs were defined according to the composite list with QT drugs known to cause torsades de pointes.[11]

Electrocardiographic findings

Preoperative 12-lead ECGs were used for determination of ECG abnormalities (paper speed 25 mm/s and calibration 10 mm/mV), including ECGs that were performed before the date of admission. All ECGs were assessed and analysed by a trained reviewer (SJ). If any doubts were present, a cardiologist (RWK/FJL) decided on the final scoring. One in four ECGs were randomly checked by RWK. ECGs that showed a pacemaker rhythm were excluded from further analysis beyond assessment of potential pacemaker malfunction, as conduction intervals are usually distorted in these ECGs due to placement of the pacemaker lead.

Clinically relevant ECG findings were defined as: quantitative findings (ventricular rate, conduction intervals and electrical axis), rhythm and conduction abnormalities, electrical axis and voltage abnormalities, ectopic beats, QRS morphology and pathological Q wave and ST-T segment abnormalities. Information concerning ventricular rate, PR interval, QRS duration and electrical axis was taken from the automated ECG analysis. The QT interval was measured manually and corrected for rate by Bazett's formula. Sinus tachycardia was defined as sinus rhythm with a rate of > 100 beats/min. Sinus bradycardia was defined as sinus rhythm with a rate of < 60 beats/min. Abnormally prolonged QTc interval was defined as a QTc interval of > 450 ms in males and > 470 ms in females.[12]

Statistical analysis

To assess differences between cases and controls, paired t-tests were used for continuous variables and McNemar's test for dichotomous variables. For non-normally distributed continuous data, the Wilcoxon signed-rank test was used. For associations, ORs were calculated through conditional multivariate logistic regression analysis. A hierarchical modelling strategy was used, in

which the first model contained the main determinant only (ECG abnormality) and the final model included potential confounders. The following covariates were considered potential confounders: age, time between ECG and surgery, CCI, use of mobility aid, previous fall, hemiplegia, impaired cognition and use of psychotropic drugs. A p-value of < 0.05 was used as threshold for statistical significance. For ECG abnormalities, the Bonferroni correction was used to adjust for multiple testing. Statistical analyses were performed using IBM SPSS Statistics (Version 19.0 for Windows. IBM Corp. Released 2010. Armonk, NY).

RESULTS

The total cohort consisted of 3505 consecutive patients who underwent hip surgery between January 1996 and May 2011. Of those, 1894 met the inclusion criteria. Within this eligible cohort, we were able to match 444 cases (311 females, mean age 70.9 years [SD 9.3]) to 444 controls (311 females, mean age 70.8 years [SD 9.2]). Further details on inclusion are shown in *figure 1*. Of the cases, 305 patients underwent surgery for a femoral neck fracture, 129 for intertrochanteric fracture and 11 for subtrochanteric fracture. Among the controls, 431 underwent total hip replacement for osteoarthritis and 12 for avascular necrosis.

Baseline characteristics are shown in *table 1*. Cases and controls showed significant differences in age, time of ECG to surgery and CCI. Use of mobility aid, hemiplegia and

Figure 1. *Inclusion flow chart*

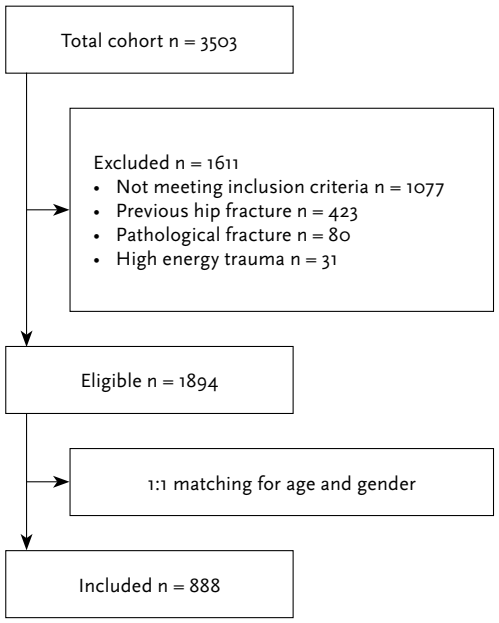


Table 1. *Baseline characteristics of hip fracture patients and controls*

	Cases n = 444	**Controls n = 444**	***P***
Age (years)	70.9 (± 9.3)	70.8 (± 9.2)	0.012
Gender, female	311 (70.0%)	311 (70.0%)	1.000
Time of ECG to surgery (days)	0.8 (0.4; 1.6)	31.9 (6.1; 68.8)	< 0.001
Comorbidity			
Charlson Comorbidity Index	1.4 (± 1.8)	0.8 (± 1.3)	< 0.001
Use of mobility aid	46 (10.4%)	145 (32.7%)	< 0.001
Previous fall	29 (6.5%)	13 (2.9%)	0.020
Visual impairment	36 (8.1%)	30 (6.8%)	0.539
Coronary artery disease	58 (13.1%)	46 (10.4%)	0.281
Hypertension	102 (30.0%)	104 (23.4%)	0.944
Heart failure	34 (7.7%)	13 (2.9%)	0.003
Cerebrovascular accident	59 (13.3%)	25 (5.6%)	< 0.001
Heart valve disorder	18 (4.1%)	29 (6.5%)	0.144
Atrial fibrillation	28 (6.3%)	19 (4.2%)	0.243
Pacemaker or ICD insertion	5 (1.1%)	7 (1.6%)	0.774
Hemiplegia/ paraplegia	22 (5.0%)	3 (0.7%)	< 0.001
Parkinsonism	26 (5.9%)	6 (1.4%)	0.001
Cognitive impairment	55 (12.4%)	1 (0.2%)	< 0.001
Alcohol abuse	42 (9.5%)	7 (1.6%)	< 0.001
Diabetes mellitus	69 (15.5%)	33 (7.4%)	< 0.001
COPD	52 (11.7%)	30 (6.8%)	0.020
Drug use			
Number of drugs	3.7 (± 3.3)	3.4 (± 2.9)	0.269
Number of psychotropic drugs	0.4 (± 0.7)	0.3 (± 0.6)	0.008
Number of cardiovascular drugs	1.0 (± 1.3)	0.97 (± 1.2)	0.752
Antiarrhythmic agents	49 (11.0%)	32 (7.2%)	0.075
Diuretics	82 (18.5%)	71 (16.0%)	0.419
Beta blockers	83 (18.7%)	87 (19.6%)	0.818
Calcium channel blockers	47 (10.6%)	51 (11.5%)	0.762
ACE inhibitors	64 (14.4%)	71 (16.0%)	0.606
Lipid lowering drugs	62 (14.0%)	72 (16.2%)	0.437

ICD = internal cardiac defibrillator; COPD = chronic obstructive pulmonary disease; RAAS = renin-angiotensin-aldosterone system; FRID = fall risk increasing drugs.
Data are *n* (%), mean (SD) or median (IQR).

cerebrovascular accident were more prevalent in cases than controls. Other common fall risk factors, such as previous fall, visual impairment, parkinsonism, alcohol abuse and cognitive impairment, were more prevalent among cases. Medical history of heart failure was significantly more prevalent in cases than controls, but medical history of other cardiovascular conditions such as hypertension, coronary artery disease and atrial fibrillation was equal in both groups. Use of psychotropic drugs was more common in cases, use of other drugs was equal in the two groups.

Table 2 shows the proportion of ECG findings and abnormalities in cases and controls. Four cases and five controls showed pacemaker rhythm and were therefore excluded from further ECG analyses. None of the paced ECGs showed signs of pacemaker malfunction. Because of the paired character of the analysis, 18 patients were therefore excluded from analysis, yielding a population of 435 cases and 435 controls for ECG analysis.

Cases and controls showed significant differences in the occurrence of several rhythm and conduction abnormalities: abnormal QTc prolongation (22.1% of cases vs. 4.8% of controls), sinus bradycardia (4.1% of cases vs. 18.4% of controls), sinus tachycardia (10.8% of cases vs. 2.1% of controls) and atrial fibrillation or flutter (6.2% of cases vs. 2.9% of controls). Electrical axis and voltage abnormalities that were significantly different between cases and controls were: right-axis deviation (2.8% of cases vs. 0.5% of controls), low QR voltage (4.8% of cases vs. 0.9% of controls) and left ventricular hypertrophy (5.3% of cases vs. 2.3% of controls). Pathological Q waves were more frequently observed in cases (8.7% of cases vs. 4.6% of controls), as were non-specific ST-T changes (21.6% of cases vs. 13.1% of controls).

Table 2. *ECG abnormalities in hip fracture patients and controls*

	Cases n = 435	Controls n = 435	p	#
Quantitative findings				
Heart rate (BPM)	81.8 (± 16.8)	70.7 (± 13.1)	< 0.001	#
PR interval (ms)†	170.0 (± 30.4)	162.2 (± 30.4)	< 0.001	#
QRS duration (ms)	93.0 (± 18.9)	94.6 (± 17.3)	0.186	
QTc interval (ms)	442.9 (± 30.7)	423.5 (± 33.5)	< 0.001	#
Conduction and rhythm abnormalities				
1st degree AV block†	34 (8.6%)	41 (10.4%)	0.489	
Abnormal QTc prolongation[1]	96 (22.1%)	21 (4.8%)	< 0.001	#
Sinus bradycardia	18 (4.1%)	80 (18.4%)	< 0.001	#
Sinus tachycardia	47 (10.8%)	9 (2.1%)	< 0.001	#
Atrial fibrillation/ flutter	27 (6.2%)	12 (2.9%)	0.024	
Supraventricular tachycardia	4 (0.9%)	1 (0.2%)	0.375	
Electrical axis and voltage abnormalities				
Left-axis deviation[2]	55 (12.8%)	41 (9.5%)	0.184	
Right-axis deviation[2]	12 (2.8%)	2 (0.5%)	0.013	
Low QRS voltage	21 (4.8%)	4 (0.9%)	0.001	#
Left ventricular hypertrophy	23 (5.3%)	10 (2.3%)	0.035	
Right ventricular hypertrophy	1 (0.2%)	0 (0%)	1.000	
Atrial hypertrophy	10 (2.3%)	7 (1.6%)	0.629	
Ectopic beats				
Premature atrial complex	24 (5.5%)	21 (4.8%)	0.766	
Premature ventricular complex	26 (5.9%)	17 (3.9%)	0.222	
Bundle branch abnormalities				
Intraventricular conduction delay	49 (11.2%)	51 (11.7%)	0.920	
Left anterior fascicular block	11 (2.5%)	9 (2.1%)	0.824	
Right bundle branch block	15 (3.4%)	15 (3.4%)	1.000	
Incomplete right bundle branch block	4 (0.9%)	8 (1.8%)	0.388	
Left bundle branch block	12 (2.7%)	9 (2.1%)	0.664	
Incomplete left bundle branch block	4 (0.9%)	2 (0.5%)	0.687	
Bifascicular block	5 (1.1%)	4 (0.9%)	1.000	
Trifascicular block	1 (0.2%)	4 (0.9%)	0.375	
Q wave and ST-T segment abnormalities				
Pathological Q wave	38 (8.7%)	20 (4.6%)	0.025	
Inverted T waves	15 (3.4%)	6 (1.5%)	0.078	
Nonspecific ST-T changes	94 (21.6%)	57 (13.1%)	0.003	
ST-segment elevations and depressions	1 (0.2%)	1 (0.2%)	1.000	

[1]Abnormal QTc prolongation: male > 450 ms, female > 470 ms. [2]For five ECGs no electrical axis could be determined because of arm lead reversal and/or ventricular tachycardia. †For 41 ECGs, the PQ interval could not be measured because of distortion and/or atrial fibrillation. Nine ECGs were excluded from analysis because of pacemaker rhythm. # Significant after Bonferroni correction (p < 0.0016). Data are *n* (%) or mean (SD).

Prevalence of first-degree atrioventricular (AV) block and supraventricular tachycardia was equal in both groups, as were all bundle branch abnormalities, bifascicular and trifascicular blocks. One case had a third-degree AV block (vs. none in the control group) and left posterior fascicular block was observed in one case (vs. none in the control group).

All quantitative ECG abnormalities that were univariately associated with hip fractures were tested multivariately (*figure 2*). The following cofactors were included in the final model: age, time of ECG to surgery, CCI, use of mobility aid, previous fall, hemiplegia, impaired cognition and use of psychotropic drugs. ECG abnormalities that remained significantly associated with hip fractures after adjustment in the final model were abnormal QTc prolongation (OR 3.9 [95% CI 2.2-6.8]), sinus bradycardia (0.3 [0.1-0.5]), sinus tachycardia (5.0 [2.1-11.8]) and atrial fibrillation (2.7 [1.2-6.1]). Adjustment for use of QTc-prolonging drugs did not alter odds ratios between abnormal QTc prolongation and hip fractures.

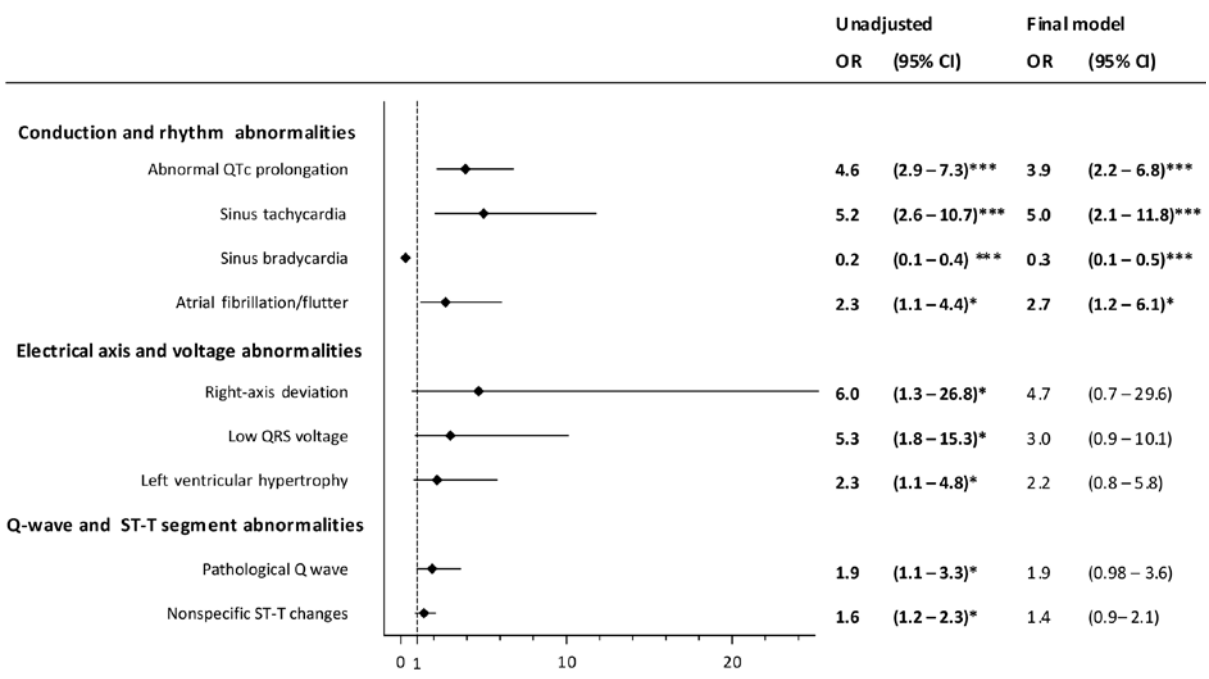
DISCUSSION

Our study showed that clinically relevant rhythm and conduction abnormalities, such as atrial fibrillation, QTc prolongation, sinus bradycardia and tachycardia, were associated with hip fractures in patients undergoing hip surgery.

An association between atrial fibrillation and hip fractures has not been shown before. Two recent studies, however, found atrial fibrillation to be an independent risk factor for falls in older patients.[13,14] Our results support this finding, as > 90% of hip fractures are due to a fall.[14] Atrial fibrillation can lead to decreased cardiac output because of an increased ventricular rate, irregular ventricular response and loss of the atrial kick. Furthermore, atrial fibrillation is associated with decreased baroreflex sensitivity, which can result in a decrease in orthostatic tolerance.[15,16] Since orthostatic hypotension is a cause for syncope and falls in older persons, this may provide an extra pathophysiological explanation for the association between atrial fibrillation and falls.

Abnormal QTc prolongation was also associated with hip fractures. QTc prolongation can cause torsades-de-pointes, which in turn can lead to syncope.[17] Ventricular tachyarrhythmias may contribute to syncope as the cause of a fall. Nevertheless it is unlikely that all patients with traumatic hip fractures suffered from torsades. Although speculative, it is possible that the effects of acute-phase response due to hip fracture or poor general condition contributed to QTc prolongation through as yet unknown

Figure 2. *Association between ECG abnormalities and hip fractures*



Final model: adjusted for age, time of ECG to surgery, CCI, use of mobility aid, previous fall, hemiplegia, impaired cognition and use of psychotropic drugs.
95% CI = 95% confidence interval.

mechanisms. A previous study has found an association between QTc prolongation and increased C-reactive protein levels which supports this theory.[18]

To our surprise, we found that study controls had a higher prevalence of sinus bradycardia on the ECG, whereas patients with hip fractures significantly more often showed sinus tachycardia. This difference may be explained by the fact that hip fracture patients will more often have an increased heart rate due to pain, anaemia and stress, leading to sinus tachycardia, or to the finding of sinus rhythm in patients who would normally have sinus bradycardia. Use of beta blockers, which potentially could have explained this finding as well, did not change the results in a multivariate model.

Univariately, we found that other markers for decreased cardiac function were associated with hip fractures, namely low QRS voltages, inverted T waves, non-specific ST-T changes, pathological Q waves and left ventricular hypertrophy. As these abnormalities are usually the result of either previous myocardial damage (e.g. due to ischaemia) and/or heart failure, patients with these abnormalities could be prone to (near) syncope when physical demands outweigh the capability of the heart to generate the required cardiac output. Three large population cohort studies found that the risk of (hip) fracture was significantly increased in patients after a diagnosis of heart failure.[19-21] Although markers for decreased cardiac function were only univariately associated with hip fractures in our cohort, this trend is in line with the findings of these population cohort studies.

Many of the potential explanatory findings in rhythm or conduction abnormalities such as complete heart block, severe bradycardias or tachycardias that may cause syncope can be transient and therefore be missed on the admission ECG. Abnormalities in ECG findings that were significantly more prevalent in hip fracture patients are by themselves not an explanation for a fall, but may be considered as 'proxies' for an abnormality that can cause a fall or syncope. However, this was not the case for conduction abnormalities. A complete third-degree heart block can be suspected when less advanced block is observed such as a bifascicular or trifascicular block, first or second degree AV block, but this was only present in a small number of subjects. It can therefore only potentially explain the fall in a small minority of patients.

Some limitations must be mentioned. One limitation of this study is the design. Although registration of all patients was performed prospectively, detailed data on comorbidity and drug use were collected from the medical records, and we can therefore not rule out incomplete data collection during admission. It is known that retrospective collection of data on falls is less reliable than prospective collection.[22] However, there is little reason to assume that missing data are differential for the groups, and therefore potential confounding by indication is unlikely. Another limitation is the fact that we compared patients in an acute setting with study controls in a more stable situation. This reflects in differences in median time from ECG to surgery between the two groups. ECGs for hip fracture patients were more often performed directly preoperatively or on the day of admission, whereas ECGs for patients undergoing planned hip surgery were more often taken during preoperative assessment by anaesthesiologists in the outpatient department. For most of the hip fracture patients, the ECG recording was performed after the actual outcome event (hip fracture). As some of the ECG abnormalities that we found (e.g. atrial fibrillation and sinus tachycardia) are known to be elicited by stress,[23] the increased prevalence of these abnormalities in hip fracture patients could be partly due to the stress of the hip fracture. To account for the differences in timing of the ECG we adjusted for time of ECG to surgery in our analyses. As it is questionable whether hospital populations are fit to serve as controls because controls should preferably resemble the general population, we hypothesised that patients undergoing planned hip surgery would resemble the general population most.[24] Also, as the prevalence of ECG abnormalities in our control group was similar to ECG abnormalities found in the general population, we believe that our control group was adequate to make meaningful comparisons.[25,26] Finally, we used Bazett's formula for correction of the QT interval for heart rate, as it is the most frequently used formula in clinical practice. However, it is known that this correction method can overestimate QT interval at higher heart rates,[27] and we should take this into consideration when interpreting the results of this study.

Hip fractures, with their associated morbidity and mortality, are among the most feared consequences of falls, and recognition of potentially modifiable risk factors in this group is therefore of great importance. The results of our study show that hip fracture patients are at much higher risk for heart rhythm and conduction abnormalities than a matched cohort of patients undergoing hip surgery for other indications.

Thus, a higher degree of caution and observation during perioperative management is warranted, as well as increased awareness of the need to undertake cardiovascular fall risk assessment when an older adult presents with one of these ECG findings to potentially reduce the risk of future falls. Further research, however, is warranted to confirm our findings in a prospective study. Additionally, it is necessary to study the effects of treatment of these abnormalities on fall incidence rates and fall-related morbidity and injury.

ACKNOWLEDGEMENTS

We thank Ms. Annemiek Schutte, Ms. Roos van der Zwan, Ms. Laura van Iersel and Ms. Judith Kwakman for their assistance in data collection.

DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Differences in interpretation of haemoglobin A1c values among diabetes care professionals

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ABSTRACT

Background: To assess the expected precision of HbA_{1c} measurements and the magnitude of HbA_{1c} changes eliciting the advice to change treatment among diabetes care professionals.

Methods: A seven-item questionnaire was sent to participants through a website. The survey focused on physicians and nurses involved in diabetes care.

Results: In total, 104 physicians, 177 diabetes specialist nurses, and 248 primary care nurses responded to the survey. A large number of the nurses (44%) and only a small number of the physicians (4%) were not aware of the inherent uncertainty of HbA_{1c} results. Nurses considered adjusting therapy based on very small changes in HbA_{1c} whereas physicians in general adhere to 0.5% (5.5 mmol/mol) as a clinically meaningful cut-off point. After therapy adjustment, a very small (0.1%) or no increase in HbA_{1c} was considered to be significant enough to conclude that glucose regulation has worsened by 49% of the nurses and only 13% of the physicians.

Conclusion: Significant differences exist in the interpretation of changes in HbA_{1c} results between physicians and nurses. Nurses consider therapy changes based on very small changes in HbA_{1c}, whereas physicians preferably agree to the clinically relevant change of 0.5% (5.5 mmol/mol). Changing therapy based on relatively small changes in HbA_{1c} might lead to undue adjustments in the treatment of patients with diabetes. There is a clear need for more training for all diabetes care professionals about both the clinical significance and accuracy of HbA_{1c} measurements.

KEYWORDS

Glycated haemoglobin, interpretation, healthcare professionals, nurses, physicians

INTRODUCTION

Both in subjects with type 1 and type 2 diabetes mellitus, adequate glucose control is considered of major importance.[1] The degree of glucose control can be assessed by frequent home blood glucose measurements, but the most widely acknowledged and reliable assessment is the measurement of the concentration of glycated haemoglobin (HbA_{1c}).[2] As such, HbA_{1c} is one of the main parameters with regards to glucose control in most outcome studies.[3,4] Therefore, most diabetes care professionals rely (at least in part) on HbA_{1c} levels to decide whether or not to recommend treatment changes to patients.

Still, HbA_{1c} measurement, and thus the interpretation of results, has its pitfalls. The analytical performance of the HbA_{1c} assay is an important factor in the overall performance of the HbA_{1c} assay.[5,6] Not all laboratories may be able to measure HbA_{1c} precisely enough to allow an outcome within 0.5% (5.5 mmol/mol) of the actual value.[6] For example, in the Netherlands, initiation of insulin therapy would be considered in a person with type 2 diabetes mellitus with an HbA_{1c} > 7.0% (53 mmol/mol) on maximal oral therapy, at least based on the advice in the 2006 primary care guideline which was the prevailing document at the time of this survey.[7]

Currently, limited data are available on how healthcare professionals perceive the accuracy of the HbA_{1c} assay and how they adjust therapy based on consecutive changes in HbA_{1c}. One study demonstrated that the majority of general practitioners presumed a high (analytical) performance of the assay without considering the biological variation, and acted on even small differences in subsequent HbA_{1c} measurements.[8] Studies assessing the difference between various healthcare professionals, including physicians and nurses, with respects to interpretation of (changes in) HbA_{1c}, are lacking.

The aim of this study was to assess the daily practice regarding the interpretation of HbA_{1c} results, i.e. the expected precision of HbA_{1c}, and the magnitude of HbA_{1c} changes possibly eliciting the advice to change treatment. Therefore, we surveyed a group of diabetes care professionals regarding these aspects.

MATERIALS AND METHODS

Design

In this cross-sectional descriptive study, an internet survey was used to collect data. The study was part of a larger survey regarding the frequency of self-monitoring of blood glucose recommended by professionals and was carried out from March to June 2010.[9] Respondents were asked to indicate their profession (physician, diabetes specialist nurse or primary care practice nurse, P, DSN and PCPN, respectively). The remainder of the questionnaire included six questions regarding the use and interpretation of HbA_{1c}. The first question assessed the expected reliability of HbA_{1c} at a level of 7.0% (53 mmol/mol). In the other five questions, patient cases were presented assessing at what HbA_{1c} level or HbA_{1c} changes the healthcare professional would initiate or change therapy (*table 1*). In total, 6965 primary care assistants, diabetes specialised nurses and doctors from the database of the Langerhans Medical Research Group were invited by email to participate in this survey. The Langerhans Medical Research Group is the research division of the Langerhans Foundation, a national diabetes organisation that organises educational activities for diabetes care professionals. The database contains information and email addresses of diabetes care professionals who are interested in the activities that are organised by the Foundation. All professionals registered in the database were invited to take part in the survey. In addition, a message containing a link to the survey was placed on the website of the Dutch Association of Diabetes Care.

Statistical analysis

Differences in the distribution of answers between the groups (P, DSN and PCPN, respectively) were tested using Fisher's exact test. P-values < 0.05 were considered statistically significant. Comparisons between pairs of groups were adjusted for multiple testing using the Bonferroni correction. SPSS version 20 (IBM Corporation, Armonk, NY) was used for the analysis.

Table 1. *Questions / patient cases*

A. At an HbA_{1c} value of 7.0% (53 mmol/mol) I expect an uncertainty of ...
B. When someone with T2DM and < 70 years is on maximal oral therapy and you consider starting insulin, at which HbA_{1c} level do you decide to start insulin?
C. Consider someone with T1DM (< 70 years) without signs or symptoms of hypoglycaemia or hyperglycaemia. HbA_{1c} was 6.9% (52 mmol/mol) at the previous visit. After three months you get a new result. At which HbA_{1c} value would you consider and propose a treatment adjustment?
D. Consider someone with T2DM (< 70 years) without signs or symptoms of hypoglycaemia or hyperglycaemia and treated with a combination of insulin and metformin. Three months previously, the HbA_{1c} was 7.3% (56 mmol/mol). The insulin dose was increased. At which HbA_{1c} level would you consider further treatment changes?
E. Consider someone with T2DM and an HbA_{1c} value of 9.0% (75 mmol/mol). Treatment adjustments are made. How much decrease in HbA_{1c} value would you consider sufficient to allow the conclusion that glucose regulation has improved?
F. Again consider someone with T2DM and an HbA_{1c} value of 9.0% (75 mmol/mol). Treatment adjustments are made. How much increase in HbA_{1c} value would you consider sufficient to allow the conclusion that glucose regulation has worsened?

T1DM = diabetes mellitus type 1 ; T2DM = diabetes mellitus type 2.

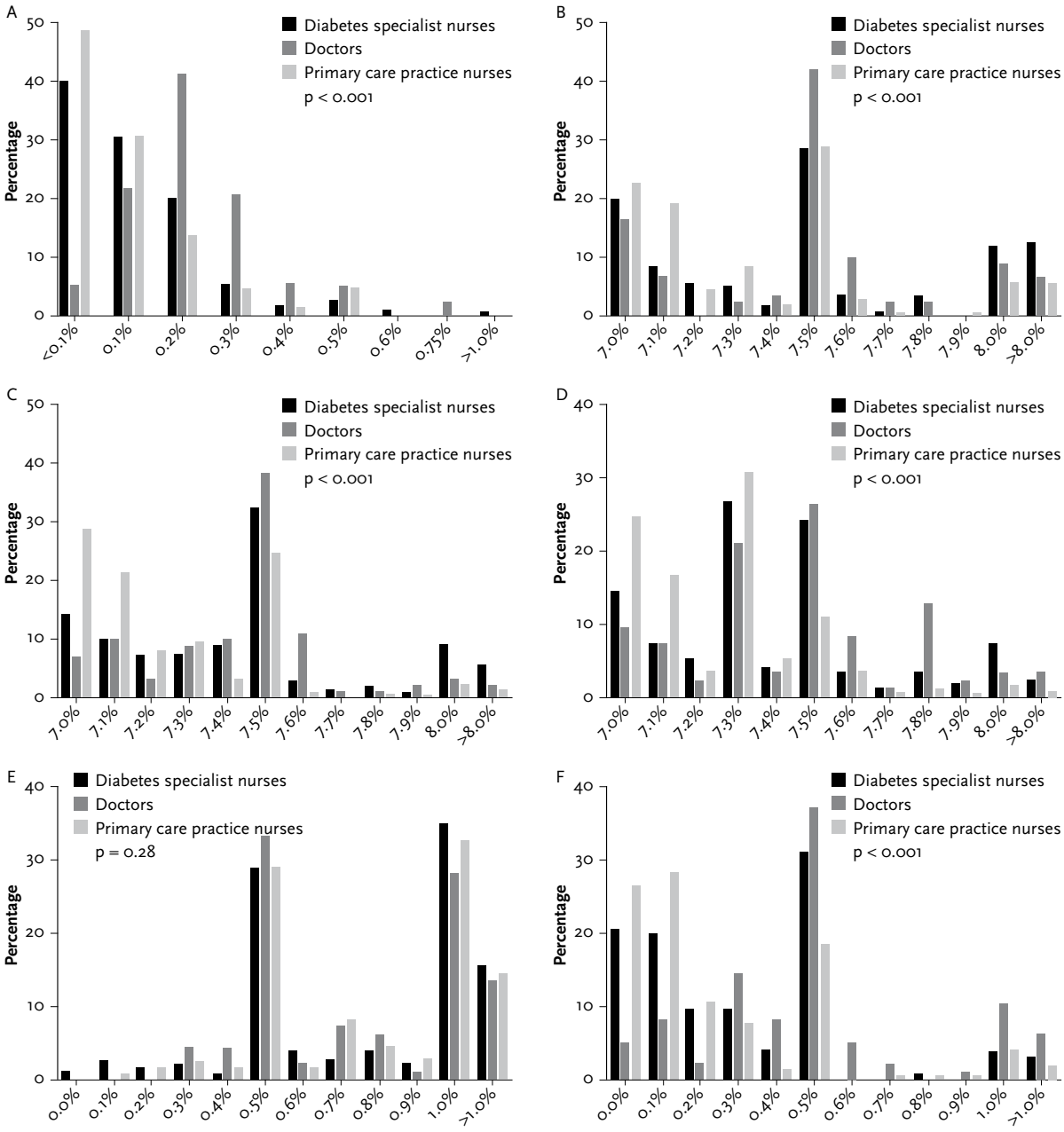
RESULTS

For this analysis, 529 healthcare professionals were included: 48 internists, 28 general practitioners, 28 paediatricians (total physicians = 104), 177 diabetes specialist nurses and 248 primary care practice nurses (total nurses = 425). The questionnaire only contained cases and questions in connection to HbA_{1c}. No questions were included detailing the demographics of the responders, except for the specific role as caregiver.

The responses to Question A (*table 1A, figure 1A*) show that a large number of the nurses (44%) and only a small number of the physicians (4%) were not aware of the inherent uncertainty of the HbA_{1c} result. When comparing the responses of the two groups of nurses, they were not significantly different from each other ($p = 0.714$, Bonferroni corrected), but each group of nurses significantly differed from the physicians ($p < 0.01$, Bonferroni corrected).

The responses to Case B (*table 1B, figure 1B*) show that a cut-off point of 7.0% (53 mmol/mol) is regarded as a signal for treatment changes by 19.8% of the healthcare

Figure 1. *Responses of the healthcare providers to the presented cases*



professionals, and a level of 7.5% (58 mmol/mol) is regarded by 32.2% of the healthcare professionals as a sufficiently powerful signal to consider starting insulin. Overall there was a significant difference in the responses between the three groups ($p < 0.001$); however, the difference between the diabetes specialised nurses and physicians was not significant ($p = 0.051$, Bonferroni corrected). Case C (*table 1C, figure 1C*) shows that a sustained HbA_{1c} level between 7.0% (53 mmol/mol) and 7.5% will prompt the vast majority (87%) of the healthcare providers to consider changing therapy in order to reach the predefined target value. Of them, 29.9% chose a level of 7.5%, in accordance with a difference of 0.6% (6 mmol/mol). Almost all other respondents (57%) chose a value between 7% and 7.4%. Overall the responses differed significantly between the groups ($p < 0.001$). PCPN were mainly responsible for this difference since they were more inclined to choose a level below 7.2%. Physicians

and DSN did not differ significantly from each other (p = 0.084, Bonferroni corrected). Case D (*table 1D, figure 1D*) provides a somewhat mixed response, with healthcare professionals tending to either start treatment changes with an HbA_{1c} which stays at a consistently higher level of 7.3% (56 mmol/mol) or, again, at the cut-off point of 7.5% (58 mmol/mol) and 7.0% (53 mmol/mol). PCPN seem more focused on trying to reach lower HbA_{1c} values than doctors (p < 0.001), specifically to reach the treatment goal of 7.0% (53 mmol/mol), whereas the responses of physicians and diabetes specialised nurses were not significantly different (p = 0.201, Bonferroni corrected). Case E addresses which change in HbA_{1c} is considered sufficient to allow the conclusion that glucose regulation has improved after treatment adjustment. A change of 1.0% (11 mmol/mol) was considered to be clinically relevant by 32.6% of the healthcare professionals, whereas 29.8% thought 0.5% (5.5 mmol/mol) was clinically relevant. There was no significant difference (p = 0.28) in responses between the different healthcare professionals (P, DSN and PCPN). Case F (*table 1F, figure 1F*) shows that especially DSN (40.0%) and PCPN (54.8%) seem to conclude that glucose regulation has worsened even when the HbA_{1c} value was the same or only slightly (0.1% (1 mmol/mol)) increased. The difference in responses between these two groups was not significant (p = 0.186, Bonferroni corrected). A major portion of the doctors (37.1%) follow the clinically relevant change of 0.5% (5.5 mmol/mol).

DISCUSSION

The results of this study indicate that nurses seem to be well aware of the importance of HbA_{1c} for the management of diabetes, but are now overly reacting to too small changes in the value of HbA_{1c} observed in their patients. This observation could partly be explained by the fact that most of the nurses consider an HbA_{1c} value to be an absolute value and are less aware of the fact that every HbA_{1c} result has uncertainty based on the analytical performance of the HbA_{1c} method used. As a consequence, nurses tend to consider treatment changes based on very small or even no differences in subsequent HbA_{1c} results. Indeed, physicians and nurses interpret HbA_{1c} differently in concluding that there is a decline or improvement of glycaemic control. A decrease of at least 0.5% (5.5 mmol/mol) or 1.0% (11 mmol/mol) at an HbA_{1c} value of 9.0% (75 mmol/mol) after adjustment of therapy is considered sufficient by all healthcare professionals to allow the conclusion that glucose regulation has improved. In contrast, a very small or no increase of HbA_{1c} is considered by most of the nurses as sufficient to come to the conclusion that glucose regulation has worsened.

In general, guidelines consider a difference of 0.5% (5.5 mmol/mol) to be clinically significant.[1,7] However, a recent study showed that the analytical performance of some HbA_{1c} assays may not be accurate enough to sufficiently support treatment decisions in the management of patients with diabetes when differences in serial HbA_{1c} measurements amount to 0.5% (5.5 mmol/mol) or less.[6] Combining this with the outcome of this survey, we can conclude that many of the nurses may react to HbA_{1c} outcome variations based on the variability of the HbA_{1c} method used instead of the true changes in the degree of glucose control. As a consequence, this could lead to undue treatment changes with accompanying costs and/or inconvenience for the patient. Furthermore, several studies have confirmed that, especially for older patients, the benefit of lowering the HbA_{1c} value at all costs (including patient inconvenience) is limited and may even lead to a higher mortality rate.[10,11]

Average HbA_{1c} of patients with diabetes in primary healthcare in the Netherlands is amongst the lowest in the world,[12] and studies such as the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study showed very clearly that strictly controlled patients have a lower risk of developing microvascular and macrovascular complications.[3,4] We believe that every healthcare professional should be supplied with the information they need to interpret HbA_{1c} values properly. The reference change value which is defined as the critical difference between two consecutive HbA_{1c} measurements representing a significant change in health status might be a valuable tool.[13,14] The analytical performance of different HbA_{1c} methods ranges from poor (most of the point of care instruments and some immunoassays) to state of the art (newer version cation-exchange HPLC methods).[15,2] It is not realistic to assume that every healthcare professional is aware of the analytical performance of every HbA_{1c} method, not even if the method used by the main laboratory is state-of-the-art. Laboratory directors or other decision makers are responsible for the choice of the HbA_{1c} method. This choice is based on many factors such as analytical performance (which is hopefully the most important factor), sample throughput (commercial laboratories), costs per test, support of and contact with the manufacturer etc. The reference change value provides insight into the impact of poorly performing methods.

One of the limitations of this study is that only healthcare providers in the Netherlands were invited to participate in this survey. Since healthcare systems may be organised differently in different countries, the results presented here may preclude generalisation. An international survey among different healthcare providers should be performed to confirm our findings. Furthermore, a limitation of the present study is the low response to the internet survey.

This limited response may have led to a non-response bias. Unfortunately, data on the characteristics of the non-respondents could not be compared with the characteristics of responders, since demographic data were lacking for both groups, thus preventing proper assessment of the magnitude of this potential bias.

In conclusion, significant differences in interpretation of (changes in) HbA_{1c} results between physicians and nurses exist. Nurses consider therapy changes based on very small changes in HbA_{1c}, whereas physicians preferably agree to the clinically relevant change of 0.5% (5.5 mmol/mol). Changing therapy based on relatively small changes in HbA_{1c} might lead to undue adjustments in the treatment of patients with diabetes. There is a clear need for more training for all diabetes care professionals about both the clinical significance and accuracy of HbA_{1c} results. The authors are planning a follow-up study to further explore the observed differences between the diabetes healthcare professionals with respect to interpretation of HbA_{1c}.

ACKNOWLEDGMENTS

The authors thank the nurses and physicians who were willing to participate in this survey and Dr. Nanno Kleefstra and Dr. Bas Houweling for their help to design the survey and their willingness to use their professional website (http://www.diabetes2.nl/nl/home.html) for the survey. Part of this study was presented in poster form at the 2012 Annual Meeting of the American Association for Clinical Chemistry (AACC) in Los Angeles, California, 15-19 July 2012.

DISCLOSURES

No funding was received. The authors declare no conflicts of interest.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Anticoagulant treatment of cancer patients with pulmonary embolism in the real world

Actual use of low-molecular-weight heparin in cancer

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ABSTRACT

Background: Since 2004, guidelines recommend long-term treatment with low-molecular-weight heparin (LMWH) in patients with cancer and pulmonary embolism (PE). We assessed the proportion of cancer patients with PE actually treated with LMWH and the duration of anticoagulant treatment in the Netherlands.

Methods: A retrospective cohort study in patients that were hospitalised for PE between 1998-2008. Patients with PE were selected from national hospital discharge records, after linkage to a national pharmacy database. Cancer patients with PE were matched for age, sex and year of diagnosis of PE to subjects with PE without cancer.

Results: 600 cancer patients with PE were matched to 1200 patients with PE without cancer. Long-term LMWH was prescribed in 82 (13.7%) of the cancer patients and in eight (0.7%) of the cancer-free patients ($p < 0.001$); all the other patients received vitamin K antagonists (VKA). From 1998-2008, there was an increase in the use of LMWH in cancer patients: in 2007-2008, LMWH was prescribed in 42 (32%) cases, compared with one (1.7%) of the cancer patients with PE in 1998-1999. Median duration of treatment was 5.8 months (interquartile range 3.1-8.8) in cancer patients, compared with 7.0 months (4.9-11) in patients without cancer ($p < 0.001$), a difference that persisted after adjustment for mortality.

Conclusions: Although the use of LMWH in patients with cancer and PE is increasing, in 2008, patients in the Netherlands are still mostly treated with VKA, and not with LMWH as recommended by guidelines. Cancer patients with PE on average receive shorter treatment than matched patients without cancer.

KEYWORDS

Pulmonary embolism, cancer, anticoagulant treatment

INTRODUCTION

Almost two centuries ago, Bouillaud associated the presence of cancer to the development of venous thromboembolism (VTE).[1] Since then, many studies have confirmed that malignancy increases the risk of VTE, and to a lesser extent also of arterial thrombosis.[2-5] The consequences of VTE in cancer patients cannot be underestimated, since it causes morbidity and pulmonary embolism (PE) related mortality.[6,7] While patients with VTE are usually treated with vitamin K antagonists (VKA) for 3-12 months, since 2004, international guidelines provide specific recommendations for patients with cancer and VTE, namely long-term treatment with low-molecular-weight heparin (LMWH).[8-10] These recommendations are based primarily on the results of the pivotal CLOT study, which showed a 50% reduction in the risk for recurrent VTE in the LMWH group, when compared with the VKA group.[11] Other smaller studies and two meta-analyses confirmed these findings.[12-15] Next to the superior efficacy, there are other advantages of LMWH use in cancer patients, including the more stable anticoagulant effect and the lack of need for monitoring, when compared with VKA. However, it is unclear whether the bleeding risk is lower with LMWH compared with VKA, as most studies are relatively underpowered to adequately assess this clinically important question. In general, VKA-associated bleeding risk is twofold increased in cancer patients as compared with patients without cancer.[16-18]

Although the recommendations regarding LMWH date from ten years ago, more recent studies indicate that the use of LMWH monotherapy in cancer patients is far from optimal. Using the medical records of four hospitals in the United States, Delate and colleagues showed that the use of LMWH – although increasing over the years – was still as low as 31% for cancer patients diagnosed with VTE in 2008.[19] Recent data from a cohort of 144 cancer patients with PE suggested that the use of LMWH is not much higher in Europe.[20]

An important area of uncertainty in the management of PE in cancer patients is the duration of the anticoagulant treatment. Guidelines – based on expert opinion – advise to continue treatment as long as the cancer is active.[10,21] However, no study has specifically evaluated the use of anticoagulants in cancer patients beyond six months. In the absence of supporting evidence, the choice on the duration and type of anticoagulants is left to the treating physicians who are often posed with the dilemma of a patient in the terminal phase, with a high risk for both bleeding and recurrent VTE.

The aim of this study was to evaluate the type and duration of anticoagulant treatment used in the real world in cancer patients with PE relative to PE patients without cancer.

MATERIALS AND METHODS

Study design and population

Data for this retrospective cohort study were derived from the Pharmo Record Linkage System (Pharmo Institute, Utrecht, the Netherlands; available at www.pharmo.nl). The registry includes demographic details and complete medical histories of more than two million Dutch patients based on data from community pharmacies (in-hospital pharmacies not included). These medication histories were linked to hospital admission and discharge records from the Dutch National Medical Register (LMR). Drugs were coded according to the Anatomic Therapeutic Chemical (ATC) classification. The hospital admission and discharge codes were coded according to the International Classification of Diseases Ninth Revision Clinical Modification (ICD9 CM). Data on all-cause mortality were retrieved from the Dutch Registry for Mortality, coordinated by the Central Bureau for Statistics (www.cbs.nl).

All subjects with a first hospitalisation for PE (ICD 415.1) between 1998-2008 were identified. In a previous study which used the same patient dataset, 10% of all PEs had been randomly verified, by checking whether the diagnosis had been objectively confirmed, which was the case in more than 95% of the events.[22] We excluded patients without a prescription for anticoagulants after the PE diagnosis.

Among patients with PE, cancer patients were identified based on at least one hospitalisation for cancer in the time period of two years prior to the PE and one year after the PE. Hospitalisation for cancer was retrieved with ICD9 codes: 140-199 (excluding code 176 and 181) and 200-208, including all admissions for solid and haematological cancer and melanoma and excluding all other skin cancers. Data were manually checked for all patients with a diagnosis of cancer outside the defined time range, to see if they received chemotherapeutic agents around the time of PE (two years before to one year after PE). If so, these patients were also considered to be cancer patients. Information on chemotherapy agents was available if prescribed via the local pharmacy. This included drugs under the classification 'hormones and hormone antagonists' (ATC L02...) and the antineoplastic agents (ATC L01...).

For every patient with PE and cancer, two PE patients without cancer were matched for age (± 1 year), sex and year of diagnosis of PE. The last moment of follow-up was defined as either the last date of hospitalisation in the database, or two months after the last prescription (for any indication), or the date of death, whichever date came last.

Study objectives

The primary objective was to assess the type and duration of outpatient anticoagulant treatment for PE. Anticoagulants were divided into LMWH (enoxaparin, tinzaparin, dalteparin and nadroparin) and VKA (acenocoumarol and phenprocoumon), based on ATC codes B01AA07, B01AA04, B01AB05, B01AB04, B01AB10 and B01AB06. Warfarin is not approved for use in the Netherlands and the new anticoagulants were not yet approved at the time of the study. For LMWH prescriptions, we checked each dose to see whether it was indeed therapeutic, i.e. more than 5500 anti-Xa units per day.

Normally, the duration of a medication prescription is approximately 2-3 months; therefore, conservatively, a patient was considered treated until two months after the last prescription. Subsequently, the duration of treatment was calculated by subtracting the date of PE from this date.

The secondary objective of the study was to evaluate the incidence of hospitalisations for bleeding during the entire follow-up. Bleeding was defined with ICD codes 430-432, 578, 362.81, 379.23, 599.7, 786.3, 784.7, 459, 569.3, 929.92, 998.11, 719.1 and 287.9. Unadjusted rates of bleeding were calculated, and then expressed as incidence rate per 1000 patient-years of follow-up. Furthermore, rates were assessed for untreated, LMWH-treated and VKA-treated patient-years.

Data analysis

The analyses were performed with PASW statistics version 19 (Ill) statistical software. Groups were described

using means and standard deviations for normally distributed continuous type of variables, and medians and interquartile ranges (IQR) for the non-normally distributed data. Differences between groups were tested using the t-test for data with a normal distribution or the Mann-Whitney test for non-normally distributed data. Chi-square tests were applied for comparing dichotomous and nominal data. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

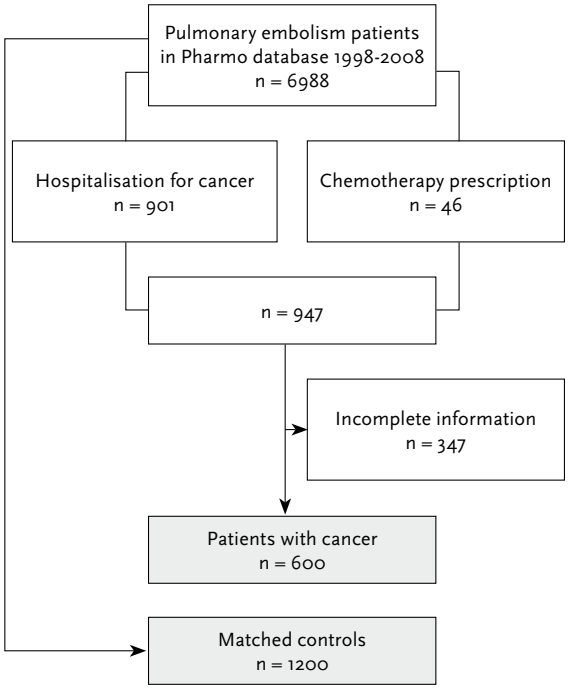
Between January 1998 and August 2008, 6988 patients were diagnosed with PE, of which 947 with cancer at the time of PE. After excluding patients for whom no prescription for anticoagulants was present in the database, 600 cancer patients with PE were eligible for the analyses: 306 women and 294 men (*figure 1 and table 1*). These patients suffered from the following types of cancer: genital/urinary tract cancer (n = 114; 19%), gastrointestinal cancer (n = 106; 18%), lung/bronchus cancer (n = 106; 18%), breast cancer (n = 99; 17%), haematological cancer (n = 51; 8.5%), brain cancer (n = 21; 3.5%), cancer of the gallbladder/pancreas/liver (n = 17; 2.8%) malignant melanoma (n = 10; 1.7%), and cancer of the bone and soft tissue (n = 6; 1.0%). Lastly, in 11 patients (1.8%) the cancer type was unspecified, or rare (lip, adrenal, conjunctivae), and 59 patients (9.8%) suffered from metastases of a non-specified or unknown primary tumour.

Table 1. *Characteristics of cancer patients with pulmonary embolism and control subjects with pulmonary embolism and without cancer*

	Cancer (n = 600)	No cancer (n = 1200)
Mean age (SD)*	66.4 (12.1)	66.4 (12.1)
Female sex (n, %)	306 (51%)	612 (51%)
Year of diagnosis of PE (n, %)		
1998	27 (4.5%)	49 (4.1%)
1999	31 (5.2%)	71 (5.9%)
2000	39 (6.5%)	76 (6.3%)
2001	39 (6.5%)	76 (6.3%)
2002	48 (8.0%)	100 (8.3%)
2003	62 (10%)	118 (9.8%)
2004	78 (13%)	158 (13%)
2005	67 (11%)	134 (11%)
2006	76 (13%)	150 (13%)
2007	75 (13%)	150 (13%)
2008	58 (9.7%)	118 (9.8%)

***Age in years; PE = pulmonary embolism; SD = standard deviation.**

Figure 1. *Flow of patients in the study*

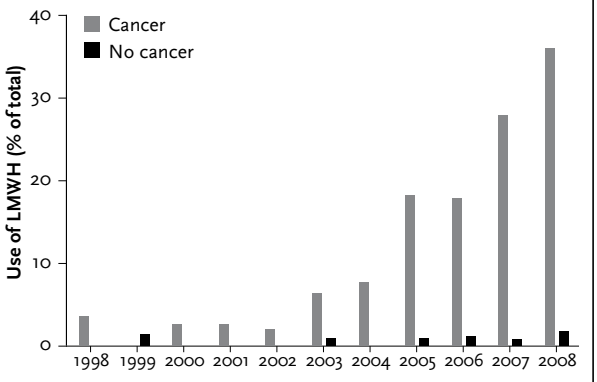


For comparison, 1200 PE patients without cancer, 612 women and 588 men, were enrolled. The median duration between the index PE event and the end of the follow-up was 14 months (IQR 6.1-36) for the cancer patients and 40 months (IQR 19-69) for those without cancer (p < 0.001).

Type of treatment prescribed for the first episode of PE

Long-term treatment of PE in cancer patients consisted of therapeutic doses of LMWH in 13.7% (82/600) of the cases, whereas this was 0.7% (8/1200) of the non-cancer patients (p < 0.001). All other PE patients were treated with VKA. When the year of diagnosis of PE was taken into account, there was a clear increase in the use of LMWH in cancer patients in the more recent years (*figure 2*; p < 0.001), but not for the patients without cancer (p = 0.76). In 2007-2008, 42/133 (32%) of the patients with cancer and PE were treated with LMWH monotherapy, compared with 1/58 (1.7%) of the cancer patients with PE in 1998-1999. Of all 82 cancer patients on long-term LMWH, 14 (17%) switched to VKA after a median time of 3.7 months (0.0-6.1), after which they were treated with VKA for a median of 2.2 months (1.9-2.4). Of the 518 cancer patients treated with VKA, 40 (7.7%) switched to LMWH after a median of 3.9 months (3.1-5.9); subsequently they were treated with LMWH for 3.2 months (2.2-6.0).

Figure 2. *Treatment with LMWH per year of diagnosis*



The Y-axis indicates the percentage of patients with PE who are treated with therapeutic doses of LMWH, at the first prescription after discharge from the hospital.

Table 2. *Rates of hospitalisations for bleeding in patients with and without cancer*

	Cancer	No cancer	p-value
Per 1000 patient-years, overall	22	11	0.0049
Per 1000 untreated-patient years	6.9	4.1	0.17
Per 1000 VKA treated patient-years	36	18	0.011
Per 1000 LMWH treated patient-years	68	0	0.018

VKA = vitamin K antagonists; LMWH = low-molecular-weight heparin.

Duration

The median duration of treatment for PE was 5.8 months (3.1-8.8) in the patients with cancer, compared with 7.0 months (4.9-11) in the patients without cancer ($p < 0.001$). A total of 116 (19%) cancer patients died after a median time of 4.9 months (IQR: 2.2-12), compared with 81 (7%) patients in the control population after a median time of 26 months (9-40; $p < 0.001$). Of all cancer patients who died, 69 (59%) died while using anticoagulant treatment. When patients who died during anticoagulant treatment were excluded from the analysis, the median duration of treatment did not significantly change (6.1 months for cancer patients vs. 7.0 months for patients without cancer, respectively).

Cancer patients on long-term LMWH were treated for a median duration of 5.1 (3.4-9.7) months, compared with 5.9 months (3.0-8.7) in the cancer patients treated with long-term VKA ($p = 0.36$). The year of PE diagnosis did not affect the treatment duration, neither in the cancer patients, nor in the control patients ($p = 0.98$).

Major bleeding

Patients with cancer were hospitalised for 29 major bleeding episodes during a median follow-up of 14 months (IQR: 6.1-36), i.e., 22 hospitalisations for bleeding per 1000 patient-years of follow-up, compared with 43 bleeding episodes in the control population during a median follow-up of 40 months (IQR: 19-69), i.e. 11 hospitalisations for bleeding per 1000 patient-years of follow-up (*table 2*), corresponding with a twofold increased risk of major bleeding in patients with cancer (OR 1.9, 95% CI 1.2-3.1). The major bleeding events occurred after a median of 5.3 months (IQR 1.3-19) in cancer patients, compared with a median of 11 months (4.4-47) in the controls ($p = 0.026$). Of the 29 major bleeding episodes in cancer patients, 18 occurred during treatment with VKA, and subsequently these patients were switched to LMWH in five cases (28%), anticoagulants were stopped in seven patients (39%) and in the remaining six patients (33%) VKA treatment was continued. Another six bleeding episodes occurred during LMWH treatment; two of these patients were switched to VKA, in one patient anticoagulants were stopped and three patients continued LMWH therapy. The remaining five hospitalisations for bleeding occurred without the use of anticoagulant treatment.

When excluding those patients who had a major bleeding episode during anticoagulant treatment, the treatment duration remained unaffected, i.e. 5.7 months in the cancer patients vs. 7.0 months in the controls.

DISCUSSION

In this study, we evaluated the clinical practice of anticoagulant treatment in a large cohort of Dutch cancer patients with PE between 1998-2008, and found that the long-term use of LMWH in cancer patients was only 14%. We observed a steady increase to 32% in 2008. Our findings are consistent with those of Delate and colleagues in a cohort of American patients. They found that in 2008, 31% of the cancer patients, received LMWH.[19] Also, our results are in line with a cohort of 141 European cancer patients with PE of which 40% received LMWH.[20]

The question arises why LMWH is underused in cancer patients despite clear recommendations in guidelines that date from nine years ago. Barriers for LMWH long-term use were studied in a small cohort of North American patients which found that in 49% of the cases the problem was represented by the insurance coverage.[23] Financial reimbursement is very unlikely to be the reason for LMWH prescription in our cohort as there is universal coverage of LMWH by insurance companies in the Netherlands.

Another explanation could be that not all treating physicians are aware of the specific treatment guidelines for cancer patients with VTE. However, in a recent survey study among different specialists, LMWH was indicated as the first choice for the long-term treatment by 82% of the respondents.[24] Alternatively, patients might have a preference for oral VKA instead of subcutaneous LMWH administration, which is not supported by evidence from qualitative studies in patients with terminal cancer.[25,26]

The present data indicate that, unexpectedly, the duration of anticoagulant treatment in cancer patients is not longer, but on average one month shorter than matched non-cancer patients with PE, which cannot be explained by a higher mortality of cancer patients during anticoagulant treatment. Unfortunately, information on the stage of cancer and chemotherapeutic treatment was not available from the dataset, which precluded assessing whether anticoagulant treatment was stopped while patients were still receiving active oncological treatment or still had active cancer.[10] Therefore, in view of the retrospective nature of the study, this finding needs to be confirmed in a prospective series of patients. Our findings, however, appear to be in line with those from previous studies reporting a median duration of treatment of 200 days,[19] with up to 77% of cancer patients with PE being treated for six months or shorter.[20] In this last cohort of hospitalised patients, the reason for stopping in 41% of the patients was death, which is much higher than in our cohort of ambulant patients. Physicians might not be aware of the specific advice with regard to the duration of treatment in cancer patients, or possibly, they might feel that the beneficial effects of anticoagulants do not outweigh the bleeding risk after six months.

Finally, we confirmed the increased risk for major bleeding in cancer patients compared with age- and sex-matched patients without cancer, in agreement with earlier reports.[16,18]

Several aspects of the present study design and results require comment. First, we included patients with pulmonary embolism in the present analysis, and no patients with deep vein thrombosis (DVT). Patients with DVT nowadays are often treated at home, while in the Netherlands most patients with PE before 2009 were treated in the hospital, according to the Dutch guideline on thrombosis treatment.[27,28] Delate and colleagues found no differences between the treatment of patients with cancer with either DVT or PE.[19] Second, to identify cancer patients, we used the definition of a hospitalisation for cancer, and manually checked to see whether they had also received chemotherapy or had been hospitalised for chemotherapy. We may have missed outpatients with cancer, with a potential selection of the more severe cases. Thirdly, this retrospective database study relied on the correct selection of patients with certain diagnoses. However, a random sample of the pulmonary embolism cases in the database was checked and correctness was confirmed in nearly all cases. Finally, we had no information about the stage of cancer and we were not able to relate the use of LMWH to the stage of disease.

In conclusion, although the use of LMWH in patients with cancer and PE is increasing, patients in 2008 are still mostly treated with VKA rather than with LMWH as recommended by major guidelines. Furthermore, most cancer patients receive anticoagulants for less than six months.

DISCLOSURES

The authors declare no conflicts of interest. No grant support was received.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Ventilator setting in ICUs: comparing a Dutch with a European cohort

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ABSTRACT

Background: From data collected during the third International Study on Mechanical Ventilation (ISMV), we compared data from a Dutch cohort with a European cohort. We hypothesised that tidal volumes were smaller and applied positive end-expiratory pressure (PEEP) was higher in the Netherlands, compared with the European cohort. We also compared use of non-invasive ventilation (NIV) and outcomes in both cohorts.

Methods: A post-hoc analysis of a prospective observational study of patients receiving mechanical ventilation.

Results: Tidal volumes were smaller (7.6 vs. 8.1 ml/kg predicted bodyweight) in the Dutch cohort and applied PEEP was higher (8 vs. 6 cm H_2O). Fewer patients admitted in the Netherlands received NIV as first mode of mechanical ventilation (7.1 vs. 16.7%). Fewer patients in the Dutch cohort developed an ICU-acquired pneumonia (4.5 vs. 12.3%, $p < 0.01$) and sepsis (5.7 vs. 10.9%, $p = 0.03$), but more patients were diagnosed as having delirium (15.8 vs. 4.6%, $p < 0.01$). ICU and in-hospital mortality rates were 19% and 25%, respectively, in Dutch ICUs vs. 26% and 33% in Europe ($p = 0.06$ and 0.03).

Conclusion: Tidal volumes were smaller and applied PEEP was higher in the Dutch cohort compared with international data, but both Dutch and international patients received larger tidal volumes than recommended for prevention or treatment of acute respiratory distress syndrome. NIV as first mode of mechanical ventilation is less commonly used in the Netherlands. The incidence of ICU-acquired pneumonia is lower and of delirium higher in the Netherlands compared with international data.

KEYWORDS

Acute respiratory distress syndrome, mechanical ventilation, outcomes mechanical ventilation, tidal volumes

INTRODUCTION

Mechanical ventilation is a technique with an extensive history. Already in the 16th century, Vesalius described his techniques for keeping an animal alive during examination of its thoracic contents by putting a tube of reed into the trachea whereby air was brought into the lungs.[1] Early mechanical ventilation in humans was described in the 18th century by Hunter, who performed ventilation using bellows to artificially ventilate drowned patients through a tracheostomy.[2] In the same century, Kite described the technique of endotracheal intubation.[3] After a period of negative pressure ventilation, induced by the invention of the iron lung in 1929, Ibsen finally introduced positive pressure ventilation outside the operating theatre in 1952. This development marked the birth of the modern intensive care unit (ICU).[4,5]

A lot of research has been conducted since then to improve mechanical ventilation, which is common practice now in critically ill patients in ICUs all over the world. This research was important because, in spite of its advantages, it became obvious that mechanical ventilation had considerable disadvantages. An important example of these is a condition observed 50 years ago which is now known as acute respiratory distress syndrome (ARDS).[6,7] Multiple studies concerning mechanisms of developing ARDS have been

conducted since then, questioning how to prevent patients receiving mechanical ventilation from developing ARDS. No clear recommendations concerning ideal tidal volumes in the prevention of developing ARDS are available, but large tidal volumes seem to be a risk factor whereas the use of lower tidal volumes seems to be beneficial.[8-12] More is known about how to treat patients with ARDS. Evidence for a strategy of mechanical ventilation with low tidal volumes was delivered in multiple studies, which showed a lower mortality when using a lung protective ventilation strategy.[9,10] Another important variable in mechanical ventilation is the applied positive end-expiratory pressure (PEEP). A certain level of PEEP is needed to achieve the optimal lung volume at which the alveoli stay open. A low tidal volume prevents damage by limiting the energy transfer into the lungs by forced inspiration.[11]

In 1998, 2004 and 2010, three large prospective cohort studies were conducted in mechanically ventilated patients in ICUs worldwide, including the Netherlands.[12,13] The main objectives of these studies were to describe the utilisation of mechanical ventilation and the outcome of mechanically ventilated patients.

Literature about recommended ventilator settings is well known among clinicians in Dutch ICUs. An influential example is the paper written by Lachmann, which maintains that a certain level of PEEP is needed to prevent damage to the alveoli.[11] We therefore questioned whether the results from the participating units in the Netherlands differ from the results in other European ICUs or not and if our ventilator settings meet the evidence-based guidelines. Our main hypothesis was that tidal volumes are smaller and applied PEEP is higher in the overall cohort of patients receiving mechanical ventilation in the Netherlands compared with the European cohort. We especially expected to find lung protective mechanical ventilation strategies in the subgroup of patients with ARDS, since an earlier study showed a decline in tidal volumes in these patients and because this strategy was implemented in ICUs in the Netherlands.[14] Furthermore we will describe the use of non-invasive mechanical ventilation (NIV) as first mode of mechanical ventilation, different modes of mechanical ventilation, sedation, and selective digestive decontamination (SDD) and outcomes, including events emerging during mechanical ventilation. We will compare these within the Dutch and European cohorts and discuss similarities and differences.

MATERIALS AND METHODS

Design

A post-hoc analysis of a prospective observational study of patients receiving invasive mechanical ventilation for at least 12 hours or NIV for at least one hour during a one-month period starting in March 2010 was conducted in 494 ICUs in Europe, USA/Canada, Latin America, Africa, Asia and Oceania. To minimise practice changes in response to observation, only the investigator and research coordinators were aware of the exact aim and timing of the study. The protocol was approved by the research ethics board of each participating institution, which decided there was no need for informed consent.[13] This article reviews only the results from the participating units from the Netherlands, compared with the results in the European cohort.

Protocol

During the study period, demographic data, daily ventilator variables, gas exchange, clinical management and complications of ventilation were recorded as well as ICU and hospital length of stay and mortality. A more extensive description of study design and protocol can be found in the original article.[13]

Statistical analysis

Data were checked for normal distribution by histogram and, when doubts arose about the normality of the distribution, by Q-Q plot. Data are expressed as median (interquartile range) and absolute and relative frequencies, as appropriate. To compare medians, the Mann-Whitney test was used. For comparing percentages, Fisher's exact test was used. Statistical analyses were performed using SPSS 16.0 and 20.0 (SPSS Inc., Chicago, IL.)

RESULTS

Characteristics of included patients

A total of 196 patients from seven ICUs were included in the Dutch cohort and 3081 patients from 185 ICUs

Table 1. *Distribution of number of patients among Dutch ICUs*

Hospital	Number of patients (% of total Dutch patients)
Medical Center Leeuwarden	30 (15.3)
Kennemer Gasthuis Haarlem	18 (9.2)
University Medical Centre Maastricht	52 (26.5)
Onze Lieve Vrouwe Gasthuis, Amsterdam	32 (16.3)
VU Medical Center, Amsterdam	30 (15.3)
Medical Center Haaglanden, The Hague and Leidschendam	24 (12.2)
Spaarne Hospital, Hoofddorp	10 (5.1)

in Denmark, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Spain, Sweden and the UK. The distribution of number of patients among Dutch ICUs is shown in *table 1*. The characteristics of the included patients are shown in *table 2*. All characteristics of the Dutch cohort are similar to the European cohort, except for the body mass index, which was lower in the Netherlands, and the admission to the ICU of patients using NIV at home, which was more common in the European cohort.

Management during mechanical ventilation

An overview of the variables related to management of mechanical ventilation is shown in *table 3*.

In the European cohort, use of NIV previous to ICU admission was more common. This also applies to NIV as first mode of mechanical ventilation, which was used in 7.1% of Dutch patients vs. 16.7% in the European cohort ($p < 0.01$). On the first day of mechanical ventilation, 34 patients (17.3%) were hypercapnic ($PaCO_2 > 48$ mmHg) in

Table 2. *Characteristics of included patients*

	The Netherlands	Europe	P-value
Participating units, n	7	185	
Patients included, n	196	3081	
Age, years	66.5 (56-75)	66 (53-76)	0.76
Female sex, n (%)	80 (40.8)	1098 (35.6)	0.15
Weight, kg	78.33 (66-89)	75 (65-85)	0.42
Body mass index, kg/m²	25.4 (23-28.6)	26.2 (23.9-29.4)	< 0.01
Simplified acute physiology score II on admission, points	45 (34-60)	44 (33-56)	0.26
Noninvasive ventilation at home, n (%)	1 (0.5)	102 (3.3)	0.02
Main reason for mechanical ventilation, n (%)			
Chronic obstructive pulmonary disease	8 (4.1)	180 (5.8)	
Asthma	1 (0.5)	17 (0.6)	
Other chronic pulmonary disease	1 (0.5)	44 (1.4)	
Neurological disease	30 (15.3)	646 (21.0)	
Metabolic, n (%‡)	4 (13.3)	103 (15.9)	
Overdose/intoxication, n (%‡)	6 (20.0)	88 (13.6)	
Haemorrhagic stroke, n (%‡)	9 (30.0)	239 (37.0)	
Ischaemic stroke, n (%‡)	2 (6.7)	82 (12.7)	
Brain trauma, n (%‡)	5 (16.7)	102 (15.8)	
Other, n (%‡)	4 (13.3)	27 (4.2)	
Neuromuscular disease	1 (0.5)	26 (0.8)	
Postoperative	63 (32.1)	724 (23.5)	
Pneumonia	20 (10.2)	259 (8.4)	
Community acquired, n (%*)	14 (70)	173 (67)	
Hospital acquired, n (%*)	6 (30)	86 (33)	
Sepsis	19 (9.7)	254 (8.2)	
Acute respiratory distress syndrome	2 (1.0)	84 (2.7)	
Congestive heart failure	14 (7.1)	280 (9.1)	
Cardiac arrest	18 (9.2)	195 (6.3)	
Trauma	5 (2.6)	144 (4.7)	
Aspiration	1 (0.5)	83 (2.7)	
Other cause of acute respiratory failure	13 (6.6)	80 (2.6)	

Data are expressed, unless otherwise stated, as median (IQR). P-value < 0.05 is ‡for neurology; *for pneumonia.

Table 3. *Variables related to management of mechanical ventilation*

	The Netherlands	Europe	P-value
NIV before admission in the ICU, n (%)	2 (1.0)	190 (6.2)	< 0.01
NIV at admission in the ICU, n (%)	14 (7.1)	516 (16.7)	< 0.01
Mode of ventilation (% of time)			
A/C	4.1	31.6	
SIMV	0.1	2.7	
SIMV-PS	0.1	5.2	
PS	50.6	23.4	
PCV	13.0	7.4	
APRV/BIPAP	20.4	12.0	
PRVC	8.7	15.3	
CPAP	1.0	1.0	
ASV	1.7	0.8	
Other mode	0.3	0.5	
Ventilator settings over the course of invasive ventilation			
Lung protective ventilation[1], n (%)	79 (40)	1089 (35.3)	0.17
Tidal volume, ml/kg PBW	7.6 (6.6-8.6)	8.1 (7.3-9.2)	< 0.01
PEEP, cm H_2O	8.0 (6.0-9.5)	6.0 (5.0-8.0)	< 0.01
In patients with ARDS			
Tidal volume, ml/kg PBW	8.6 (7.4-9.7)	7.7 (6.6-8.8)	0.48
PEEP, cm H_2O	8.25 (8.0-8.5)	9.4 (7.0-12.1)	0.58
Total respiratory rate, breaths per minute	19 (16-22)	18 (15-20)	< 0.01
Sedation, n (%)	157 (80.1)	2306 (74.8)	0.11
As % of MV-duration	66.7 (21.3-100)	50.0 (0-100)	0.05
Analgesia, n (%)	137 (69.9)	2029 (65.9)	0.28
Neuromuscular blocking, n (%)	14 (7.1)	325 (10.5)	0.15
Liberation from mechanical ventilation met criteria[2], n (%)	187 (95.4)	2703 (87.7)	< 0.01
Scheduled extubation of patients met criteria, n (%)	105 (71.4)	1514 (86.1)	< 0.01
Unplanned extubation (% of patients 'at risk'[3])	42 (28.6)	245 (13.9)	< 0.01
NIV after extubation, n (%[4])	2 (1.4)	257 (14.6)	< 0.01
Reintubation (% of patients at risk[5])	14 (9.5)	251 (14.3)	0.14
After scheduled extubation	13 (12.4)	202 (13.3)	0.88
After unplanned extubation	1 (2.4)	49 (20.0)	< 0.01
Hours until reintubation	29.5 (10.3-52.5)	25 (6.0-68.0)	0.83
Tracheotomy, n (% of patients at risk[6])	15 (7.8)	440 (14.9)	< 0 .01
Use of SDD, days per patient	2 (0-5)	0 (0-0)	< 0.01
During MV, days (% of total days with MV)	603 (65.5)	1900 (10.1)	
Days with MV and SDD	2 (0-3)	0 (0-0)	< 0.01

Data are expressed, unless otherwise notated, as median (IQR). MV = mechanical ventilation, SDD = selective digestive decontamination; NIV = non-invasive positive-pressure ventilation; A/C = assist-control; SIMV = synchronised intermittent mandatory ventilation; PS = pressure support; PCV = pressure controlled ventilation; ARPV/BIPAP = airway pressure release ventilation/biphasic positive airway pressure; PRVC = pressure regulated volume control; PEEP = positive end-expiratory pressure
1: tidal volume below 6 ml/kg predicted body weight (PBW) or tidal volume below 8 ml/kg PBW and plateau or peak inspiratory pressure less than 30 cm H_2O 2: cohort excepting patients with successful NIV, 3: cohort excepting patients with a previous tracheotomy and patients with successful NIV, 5: scheduled and unplanned extubated patients, 4: scheduled and unplanned extubated patients, 6: cohort excepting patients with a previous tracheotomy and patients with successful NIV.

the Dutch cohort, whereas this percentage was 19.4% in Europe. In the European cohort, assist control was the most used mode of invasive ventilation, followed by pressure support (31.6 and 23.4%). In the Netherlands, pressure support was the most used mode (50.6%), followed by airway pressure release ventilation/biphasic positive airway pressure (20.4%) and pressure controlled ventilation (PCV, 13.0%). In the Netherlands, synchronised intermittent mandatory ventilation (SIMV) and SIMV-pressure support were rarely used (both 0.1% of time during mechanical ventilation), with higher percentages worldwide (2.7 and 5.2% respectively).

Tidal volumes per kilogram predicted bodyweight (PBW) were significantly lower in the Dutch cohort: 7.6 ml/kg vs. 8.1 ml/kg ($p < 0.01$) and applied PEEP was significantly higher (8.0 cm H_2O vs. 6.0 cm H_2O; $p < 0.01$). The proportion of patients receiving a pressure/volume limited ventilation strategy (tidal volume below 6 ml/kg actual body weight or tidal volume below 8 ml/kg actual body weight and peak or plateau inspiratory pressure less than 30 cm H_2O) was comparable in the two cohorts: 40% in the Netherlands vs. 35% in Europe.

In Dutch ICUs the median period on mechanical ventilation was three days, of which the median duration of sedation was two days. These periods were median four ($p < 0.01$) and two ($p = 0.3$) days, respectively, in other European ICUs. The corresponding duration of sedation expressed as a percentage of mechanical ventilation duration was 66.7% in the Netherlands and 50% in the European cohort ($p = 0.05$).

In the Dutch cohort, 95.4% met the criteria for liberation of mechanical ventilation. Of these 71.4% were indeed planned extubations, of which 87.6% successfully. In other European ICUs, a larger percentage (86.1%, $p < 0.01$) of patients who met the criteria were liberated from mechanical ventilation, but the same amount of extubations were successful. Unplanned extubation was more common in the Netherlands (28.6 vs. 13.9%) and was followed by reintubation in 2.4% of the cases in the Netherlands and in 20.0% of the cases in the European cohort. After extubation, 1.4% of the Dutch patients received NIV, versus 14.3% worldwide. When reintubation was necessary, duration until reintubation did not differ between the two cohorts.

Events emerging during mechanical ventilation and mortality

The most common adverse events during mechanical ventilation in the Netherlands were fever (21%) and delirium (16%). In the European cohort, fewer patients developed delirium (5%, $p < 0.001$), but more patients were recorded as having an ICU-acquired pneumonia (9.4%, $p = 0.007$). Expressed as days with ICU-acquired pneumonia per 1000 days of mechanical ventilation, we found 28 days in the Dutch cohort and 99 days for European ICUs.

The median length of stay in the ICU in the Netherlands was four days (2-8), which was shorter than in the European cohort (six days, $p < 0.01$).

The predicted death rate was 38% for European ICU patients with a standardised mortality ratio (SMR) of 0.66 and 0.82 for ICU and in hospital mortality, respectively. Predicted death rate was 41% for Dutch ICU patients with SMRs of 0.46 and 0.58 for ICU and in hospital mortality. Actual ICU and hospital mortality after ICU admission was lower than predicted in both cohorts and higher in other European ICUs than in the Netherlands (19.4 and 25.0% compared with 25.5 and 32.7% European, $p = 0.06$ and 0.03 respectively). Mortality at day 28 after admission in the ICU was also lower in the Netherlands (18.4 vs. 24.5%, $p = 0.06$).

More detailed information concerning events emerging during mechanical ventilation and mortality can be found in *table 4*.

DISCUSSION

When comparing the study results to our hypothesis, we found that tidal volumes are indeed smaller and applied PEEP is higher in Dutch patients receiving mechanical ventilation. The difference in median tidal volumes is small though, despite its statistical significance. Concerning the median tidal volume in the Dutch cohort, another issue stands out. There is not much evidence for what the optimal tidal volumes in patients without ARDS would be, but a recent Dutch study found less patients with healthy lungs developing ARDS if they received small (6 ml/kg PBW) instead of larger (10 ml/kg PBW) tidal volumes.[15] Considering this outcome, the lower median tidal volume of 7.6 ml/kg PBW in the Dutch cohort still implies a substantial number of patients receiving larger tidal volumes. However, more research has to be done on ARDS-preventing strategies in mechanical ventilation.

In the subgroup of patients with ARDS, both Dutch and European cohorts received larger tidal volumes and applied PEEP was higher when compared with these settings in the overall study population. In both the Dutch and the European cohort tidal volumes are larger than recommended.[9,16] However, in both cohorts the subgroups of patients with ARDS were very small. Conclusions based on the aforementioned results may therefore be of limited value.

Of interest is the use of NIV in Dutch ICUs, the incidence of which is about 50% lower compared with the use of NIV in the European cohort. NIV is an especially beneficial mode of ventilation for patients with hypercapnic respiratory failure.[17] While there may have been

Table 4. *Events emerging over the course of mechanical ventilation and outcomes*

	The Netherlands	Worldwide	P-value
Events emerging during mechanical ventilation			
ARDS, n (%)	16 (9.1)	178 (6.5)	0.21
ICU-acquired pneumonia, n (%)	8 (4.5)	329 (12.3)	< 0.01
Sepsis, n (%)	10 (5.7)	290 (10.9)	0.03
Barotrauma, n (%)	1 (0.6)	47 (1.8)	0.36
Renal failure, n (%)	17 (9.7)	224 (8.4)	0.58
Fever, n (%)	42 (23.9)	545 (20.4)	0.29
Delirium, n (%)	31 (15.8)	142 (4.6)	< 0.01
Outcomes			
Duration of ventilatory support, days	3 (2-6)	3 (2-8)	0.04
Length of stay in the ICU, days	4 (2-8)	6 (3-14)	< 0.01
Length of stay in the hospital, days	16 (7-32)	18 (9-34)	0.01
Mortality, n (%)			
In the ICU	38 (19.4)	786 (25.5)	0.06
At day 28 after admission in the ICU	36 (18.4)	756 (24.5)	0.06
In the hospital	48 (25.0)	979 (32.7)	0.03

Data are expressed, unless otherwise notated, as median (IQR). ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

unaccounted differences between the patients concerned, the percentages of hypercapnia on ICU admission were comparable. While we do not know the considerations of the treating physicians concerning the choice between invasive or non-invasive ventilation, the number of hypercapnic patients would lead us to expect more use of NIV in Dutch ICUs. Not choosing NIV might be related to the presence of contraindications as unconsciousness, airway obstruction, exhaustion, apnoea or excess amounts of sputum. If no contraindications are present, NIV should be considered the first mode of ventilation, because previous studies have shown that NIV can reduce the need for endotracheal intubation, with the associated risk of complications, length of stay in the ICU and hospital and mortality.[18] Also of importance could be the weight Dutch clinicians put on the advantages of invasive mechanical ventilation, including lower work of breathing or more beneficial effects on circulation with higher possible levels of applied PEEP.

Another finding is the difference between the Dutch and European cohorts in the ventilator modes used. In the Netherlands, the most commonly used mode was pressure support, whereas in ICUs in Europe volume-controlled ventilator (VCV) modes are more commonly used. The collected data do not show an explanation for this difference. An obvious explanation would have been the use of sedation, but instead of less sedation we found sedation being more common in patients receiving mechanical ventilation in the Netherlands. In the literature, little can be found about the benefit or disadvantages of different ventilation modes in critically ill patients. More is known about ventilation modes in patients with ARDS, but still obvious preference exists concerning the mode of ventilation. Patients with ARDS may benefit from PCV when compared with VCV, but this could also have been attributed to severity of illness.[19] The substantial number of patients receiving larger tidal volumes than recommended, as mentioned above, could perhaps be explained by the mode of mechanical ventilation used. As pressure support was more often used in the Netherlands, and with pressure support tidal volumes may vary, it may be more difficult to achieve consistent tidal volumes of 6 ml/kg.

The higher prevalence of delirium in the Netherlands could have contributed to the amount of unplanned extubations, the incidence of which is high compared with both the European cohort and findings in previous literature.[20] On the other hand, less of the unplanned extubated patients were reintubated in the Dutch cohort compared with ICUs in Europe. We probably cannot draw any conclusions about this specific event, because of the small size of the Dutch cohort.

When looking at events emerging during mechanical ventilation, some prominent differences become clear. In both cohorts the percentage of patients with renal failure, defined as the need for renal replacement therapy,

was higher than the percentage present in the literature, suggesting a higher severity of illness. However, SAPS II scores at ICU admission were not higher in the Dutch cohort. A large prospective study found 4.2% of the ICU population in need of renal replacement therapy.[21] Delirium is a common finding in ICU patients, especially when they receive mechanical ventilation. When compared with findings in literature, the percentage of patients with an ICU-acquired delirium in the Dutch cohort is low and in the European cohort even lower.[22] It is questionable, however, if all patients with delirium were detected. In a recent study, concerning the Confusion Assessment Method adopted for the ICU (CAM-ICU), this method was found to have a sensitivity of only 47%.[22] The CAM-ICU is a widespread method for defining delirium, also in the Netherlands, and was used in the ICUs in the Dutch cohort. It is therefore likely that in our population not all patients with delirium were detected. We do not know the method for detection of delirium in the other ICUs in Europe. Sedation could have been of influence, because more sedation lowers delirium scores. In this study, we did not find this coincidence; sedation was even slightly more common in the Netherlands. The higher incidence of ICU-acquired pneumonia in the European cohort comes with an obvious less common use of SDD in European countries other than the Netherlands. This matches the findings in a large Cochrane review that showed an overall significant decrease in incidence of respiratory tract infections when SDD was used in patients receiving mechanical ventilation.[23] The difference in degree of SDD administration could also explain at least part of the lower mortality rates in Dutch ICUs, because the aforementioned review also showed a lower mortality rate within cohorts receiving topical and systemic SDD. The difference in mortality is probably not due to a difference in illness, according to the predicted death rates. What exactly caused the different mortality rates cannot be elucidated by this study and it is not possible to determine the share of settings in mechanical ventilation in these differences.

Limitations of the study

In spite of some conspicuous findings, the results of the Dutch cohort discussed in this article might not be completely accurate for common practice in Dutch ICUs. Collection of data was indeed conducted in all ventilated patients during one month, which provides an overview of common practice in ICUs in the Netherlands. However, data were collected in only seven ICUs, which is quite a small number of participating ICUs compared with the total amount of ICUs (about 100) in the Netherlands. Another limitation of the presented data is the moment of collection. This article is based on data collected in 2010, so it is very well possible that ventilator settings in ICUs have changed since then.

CONCLUSION

In this post-hoc analysis of a large international prospective observational trial, we found tidal volumes to be smaller and applied PEEP to be higher in a Dutch cohort compared with data from a European cohort, but both Dutch and international patients received larger tidal volumes than recommended for prevention or treatment of ARDS. NIV as first mode of mechanical ventilation is less commonly used in the Netherlands. The incidence of ICU-acquired pneumonia was lower and the incidence of delirium was higher in the Netherlands compared with international data.

DISCLOSURES

The authors do not have conflicts of interest. No funding was provided.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Induction therapy with short-term high-dose intravenous cyclophosphamide followed by mycophenolate mofetil in proliferative lupus nephritis

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ABSTRACT

Background: For decades, high-dose intravenous cyclophosphamide (ivCY) given for 24-30 months was regarded as the standard therapy for proliferative lupus nephritis, despite serious side effects. Our aim was to evaluate the effect of induction therapy with short-term high-dose ivCY followed by mycophenolate mofetil (MMF) on disease parameters, mortality and health-related quality of life (HRQoL) in patients with proliferative lupus nephritis.

Methods: Between January 2003 and November 2006, 71 patients with biopsy-proven proliferative lupus nephritis were included in the second Dutch Lupus Nephritis Study. All patients were treated with ivCY (750 mg/m^2, six monthly pulses) plus oral prednisone, followed by MMF (2000 mg/day) plus oral prednisone for 18 months, and then azathioprine (2 mg/kg/day) plus oral prednisone. Study endpoints included the occurrence of renal relapse, end-stage renal disease (ESRD) and mortality.

Results: After a median follow-up of 3.8 years (range 0.1-4.5), four (5.6%) of the 71 patients had a renal relapse, one (1.4%) failed treatment, one (1.4%) reached ESRD, and two (2.8%) died. Systemic lupus erythematosus (SLE) Disease Activity Index, serum creatinine, proteinuria and antibodies against anti-dsDNA decreased significantly during treatment and serum levels of complement factor 3 and 4 increased significantly. Furthermore, six of eight domains of the Short Form-36 as well as the number of symptoms and total distress level according to the SLE Symptom Checklist improved significantly over time.

Conclusions: This open-label study shows that induction therapy with short-term (six monthly pulses) high-dose ivCY followed by MMF is effective in preventing renal relapses, ESRD and mortality and improving HRQoL in patients with proliferative lupus nephritis.

KEYWORDS

Cyclophosphamide, lupus nephritis, mycophenolate mofetil, renal relapse, quality of life

INTRODUCTION

For decades, high-dose intravenous cyclophosphamide (ivCY) given for 24-30 months was regarded as standard therapy for systemic lupus erythematosus (SLE) patients with proliferative lupus nephritis. This treatment has been

proven to be highly effective with a renal survival after ten years of approximately 80%.[1,2] However, long-term high-dose ivCY treatment is burdensome for patients and leads to an increased risk of infections, malignancies and infertility, partly depending on the cumulative dose and age of the patient.[3,4] Since patients with lupus nephritis are usually young women of childbearing age, infertility is a serious complication which can greatly affect health-related quality of life (HRQoL). Therefore, it is important to search for alternative treatments that are equally effective with respect to renal outcome, but with fewer side effects.

The second Dutch Lupus Nephritis study, which started in 2003, was originally designed as a randomised controlled trial (RCT) comparing induction treatment with short-term high-dose ivCY (750 mg/m^2, six monthly pulses) followed by mycophenolate mofetil (MMF; 18 months) to the standard regimen consisting of 24 months of high-dose ivCY. Short-term ivCY preceding MMF was chosen because at that time the efficacy of MMF as induction therapy was not established. Furthermore, at the start of the study, long-term follow-up data of low-dose ivCY, as used in the Euro-Lupus Nephritis Trial, were not available. Treatment was continued with MMF for 18 months as the high-dose ivCY National Institute of Health (NIH) scheme also spanned a period of 24 months. After 24 months, immunosuppression was continued with azathioprine.

However, the first data from the Euro-Lupus Nephritis Trial challenged long-term treatment with high-dose ivCY.[5,6] Moreover, maintenance treatment with MMF was shown to be superior to ivCY, although this was mainly due to a higher than generally observed mortality rate in the ivCY-treated patients.[7] Hence, the RCT design of the second Dutch Lupus Nephritis study was changed into an open-label cohort design, evaluating the effects of six monthly pulses of ivCY followed by MMF for 18 months.

The aim of this open-label study was to investigate the effect of induction therapy with short-term high-dose ivCY followed by MMF on renal function, mortality and HRQoL in patients with proliferative lupus nephritis.

METHODS

Patients

Between January 2003 and November 2006, 71 patients from 20 hospitals in the Netherlands were included in the second Dutch Lupus Nephritis study. All patients were aged between 18 and 70 years, fulfilled ≥ 4 American College of Rheumatology (ACR) criteria for SLE and had active proliferative lupus nephritis, defined as biopsy-proven lupus nephritis (WHO class III or IV, in combination with class V in seven patients; renal biopsy had to be performed less than one year before inclusion), active urinary sediment (> 5 dysmorphic erythrocytes per high-power field and/or presence of cellular casts) and proteinuria > 0.5 g/day. Patients with active infection, malignancy < 5 years before inclusion (except basal cell carcinoma), pregnancy or refusal to use reliable contraceptives during the first 2.5 years of treatment, or known allergy for the study medication were excluded.

The study was approved by the ethics committee (METC Utrecht) and all patients provided written informed consent according to the Declaration of Helsinki.

Treatment

All patients were treated with ivCY (750 mg/m^2) every month for a total of six pulses, in combination with mesna (natrium-2-mercapto-ethane sulphonate) to prevent bladder toxicity (60% of ivCY dose given in three infusions of 100 ml, NaCl 0.9% at -30, 240 and 360 minutes after ivCY). Oral prednisone was added (first month 1 mg/kg/day, second month 0.75 mg/kg/day, third month 0.50 mg/kg/day and then tapered by 5 mg/day every month to 10 mg/day). After six months, treatment was continued with MMF (1000 mg/twice daily) plus oral prednisone (10 mg/day) for 18 months. Subsequently, treatment was continued with azathioprine (2 mg/kg/day) plus oral prednisone (10 mg/day).

All patients were treated with angiotensin-converting enzyme (ACE) inhibitors (preferably enalapril ≥ 10 mg/day or in case of side effects angiotensin-II receptor antagonists; preferably losartan ≥ 50 mg/day), calcium (500 mg/day) and colecalciferol (800 IE/day) supplementation.

Study endpoints

Patients were evaluated monthly during the first five months and then every three months, with a maximum follow-up of four years. The primary study endpoint was the occurrence of a renal relapse. A renal relapse could occur after week 12 and was defined as a nephritic flare: doubling of the lowest obtained serum creatinine so far, and/or a proteinuric flare: development of either nephrotic syndrome (proteinuria > 3.5 g/day) while the lowest protein excretion so far had been repeatedly ≤ 2.0 g/day, or proteinuria > 1.5 g/day without other causes in a previously non-proteinuric patient. Secondary endpoints included treatment failure, end-stage renal disease (ESRD), mortality, treatment toxicity and adverse events (especially infections resulting in hospitalisation and herpes zoster virus infections). Treatment failure was defined as doubling of baseline serum creatinine confirmed on two consecutive visits excluding other causes. Treatment toxicity was defined as discontinuation of treatment due to adverse events which made appropriate dosing of the drug impossible.

In addition, the number of patients achieving response was analysed. Complete response included no disease activity, defined as proteinuria < 0.5 g/24 hours and serum

creatinine within 125% of the baseline value at 5-12 months after the start of induction therapy. Partial response was defined as an improvement not sufficient for the definition of complete response, i.e. reduction of proteinuria of > 50% (and at least < 3 g/24 hours) and serum creatinine within 125% of the baseline value at 5-12 months after the start of induction therapy.[8]

Clinical, laboratory, and HRQoL assessments

At all visits, serum creatinine, proteinuria, anti-double-stranded DNA antibodies (anti-dsDNA), complement factor 3 (C3), complement factor 4 (C4) and current medication were recorded. Anti-dsDNA positivity was assessed according to local standards. Disease activity was measured using the SLE Disease Activity Index (SLEDAI), ranging from 0 to 105.[9] Furthermore, physicians were asked to score disease activity on a visual analogue scale (VAS; ranging from 0 to 10) at baseline. For both measures, a lower score denotes less disease activity.

HRQoL was assessed yearly with several questionnaires. The SLE Symptom Checklist (SSC) was used to study the presence and perceived burden of both disease-related and treatment-related symptoms. The SSC refers to the past month and consists of 38 symptoms. Each item is scored on a frequency scale, and if the symptom is present, also on a discomfort scale: 4-point Likert scale, ranging from 1 = present, but not burdensome to 4 = extremely burdensome. The total distress level is calculated as the sum of the perceived burden of each symptom present (range 0-152).[10]

The Short Form-36 Health Survey (SF-36) was used as a generic measure of HRQoL. It contains 36 questions, evaluating eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. For each domain, the scores are summed and recoded into a scale from 0 to 100, with a higher score representing better functioning and/or fewer limitations.[11,12] Physical component summary and mental component summary are calculated as summary health scores.[13]

The Dutch shortened version of the Profile of Mood States (POMS) was used to measure emotional well-being. It refers to the past days, including today, and covers one positive and four negative mood states: vigour (5 items), depression (8 items), fatigue (6 items), anger (7 items) and tension (6 items). For each mood state, the scores on a 5-point response format, ranging from 0 = not at all to 4 = extremely, are summed.[14,15]

An adapted version of the Influence of Rheumatic Diseases on General Health and Lifestyle (IRGL) questionnaire, based on the Arthritis Impact Measurement Scale (AIMS), was used to study the effect of SLE on activities of daily life. For the present study, only the subscales mobility (six items) and impact of disease (ten items) were used. The IRGL refers to the past month. For each subscale, the scores on a four-point Likert scale, ranging from 1 = almost never to 4 = almost always, are summed. A higher score represents better mobility and more effect of disease, respectively.[16]

Statistical analysis

Results were expressed as mean ± standard deviation (SD) or median (range) for normally distributed and non-normally distributed data, respectively. Generalised estimating equations (GEE) with exchangeable correlation structure were used to analyse clinical, laboratory and HRQoL assessments within subjects over time. GEE is a technique for longitudinal analysis which makes use of all available longitudinal data and allows unequal numbers of repeated measurements.[17] If residuals were

Table 1. *Baseline characteristics of 71 patients with proliferative lupus nephritis*

Female gender	55 (77%)
Caucasian	53 (75%)*
Age (years)	36.6 ± 11.7
Time since diagnosis SLE (years)	0.2 (0.0-16.0)
LN as first manifestation	37 (53%)
Hypertension[a]	50 (74%)
Systolic blood pressure (mmHg)	140 (100-190)
Diastolic blood pressure (mmHg)	82 (55-120)
Biopsy WHO class III / IV	18[†] (25%) / 53[‡] (75%)
SLEDAI	17 ± 6
Physician's VAS	7 (0-10)
Serum creatinine (µmol/l)	93 (53-435)
Anti-dsDNA positivity	57 (89%)
Serum C3 (g/l)	0.55 (0.20-1.66)
Serum C4 (g/l)	0.09 (0.01-0.53)
Low C3/C4	55 (85%)
Proteinuria (g/24h)	2.87 (0.51-19.00)
Hematuria (> 5 RBC/hpf)	64 (91%)
Leukocyturia (> 5 WBC/hpf)	44 (65%)
Cellular casts present	35 (58%)

Values are number (percentage), mean ± SD or median (range). SLE = systemic lupus erythematosus; LN = lupus nephritis; SLEDAI = SLE disease activity index; WHO = World Health Organisation; VAS = visual analogue scale; anti-dsDNA = anti-double-stranded DNA antibodies; C3 = complement factor 3; C4 = complement factor 4; RBC = red blood cells; hpf = high power-field; WBC = white blood cells; [a]systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive drugs; *non-Caucasian patients were Asian (n = 11) or Black (n = 7); [†]2/18 patients had class III in combination with class V changes; [‡]5/53 patients had class IV in combination with class V changes.

non-normally distributed, parameters were transformed (log, square root or logit) before being entered into the equation. P values < 0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

RESULTS

The mean age of the 71 patients with proliferative lupus nephritis was 36.6 years (SD±11.7), 77% were female and median time since diagnosis of SLE was 0.2 years (range: 0.0-16.0). All baseline characteristics are shown in *table 1*.

Study endpoints

In February 2009, the median follow-up was 3.8 years (range 0.1-4.5). In total, five (7.0%) of the 71 patients were lost to follow-up (week 13 to 186). During follow-up, four (5.6%) patients had a renal relapse (week 68 to 124), which consisted of doubling of the lowest serum creatinine (nephritic flare) in two patients and of proteinuric flares in two patients. Furthermore, one (1.4%) patient failed treatment (week 117), one (1.4%) reached ESRD (week 87) and two (2.8%) died. Causes of death were sepsis (week 5) and cancer (week 36) (*table 2*). Of note, four of the eight patients with renal relapse, treatment failure, ESRD or mortality were non-Caucasian.

In total, ten patients experienced treatment toxicity from CY (n = 1, patient quit the study; week 3), MMF (n = 1, patient switched to azathioprine), or azathioprine (n = 8, seven patients switched back to MMF and one patient continued with oral prednisone alone). Serious infections occurred in 15 patients, of which eight had a herpes zoster virus infection. In addition to the patient who died from cancer (anaplastic T-cell lymphoma), one other patient developed cancer (testicular seminoma) and five patients suffered from avascular necrosis of the hip (n = 3) or knee (n = 2) during follow-up.

Of the 71 patients, 42 achieved complete response, 15 achieved partial response and six did not achieve complete or partial response after short-term high-dose ivCY. The remaining patients reached a study endpoint within the first five months (n = 2), had no available data on both serum creatinine and proteinuria at baseline and after 5-12 months (n = 4), or were lost to follow-up (n = 2).

After high-dose ivCY, 65 patients switched to MMF plus oral prednisone. After two years, 57 patients switched to azathioprine plus oral prednisone, one patient switched to oral prednisone alone, and two patients stayed on MMF plus oral prednisone (reasons unknown) (*figure 1*).

Clinical and laboratory assessments

SLEDAI score, serum creatinine and proteinuria decreased significantly and serum levels of C3 and C4 increased significantly during treatment (*figure 2*). At baseline, 89% of patients had antibodies against anti-dsDNA and this percentage decreased significantly over time (51% after four years of treatment).

The changes in generic and disease-specific HRQoL during follow-up are shown in *figures 3* and *4*, respectively. Data on at least one time point were available for 62 of the 71 (87%) patients, with a median follow-up of 3.0 years (range 0.0-4.1).

Six of the eight domains of the SF-36 (physical functioning, role-physical, bodily pain, social functioning, role-emotional and mental health) as well as the physical component summary improved significantly over time. No overall significant effect of treatment was found on vitality, general health or the mental component summary. For the POMS, tension decreased significantly during treatment, but no significant effect was found on the other mood states.

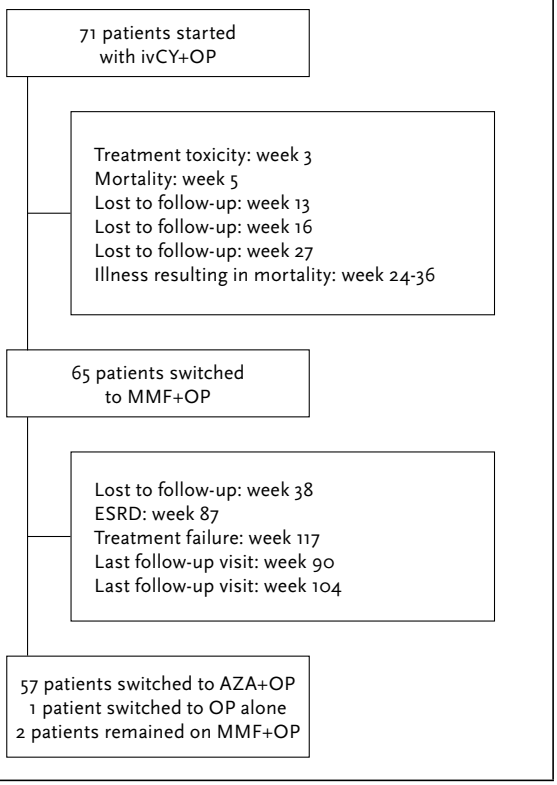
The number of symptoms and total distress level according to the SSC improved significantly during treatment. Fatigue (92%), painful joints (78%) and chubby cheeks/face (75%) were the most frequently reported complaints at baseline. The percentage of patients who reported to be fatigued decreased only slightly over time (85% after four years of

Table 2. *Proportion of 71 patients with proliferative lupus nephritis reaching study endpoints*

Years of follow-up	3.8 (0.1-4.5)
Lost to follow-up	5 (7.0%)*
Renal relapse	4 (5.6%)
- Doubling of lowest serum creatinine	2
- Proteinuric flare	2
- Both	-
Renal relapse rate[a]	1.8
ESRD	1 (1.4%)
Death	2 (2.8%)
Infection rate[a]	7.8
- HZV infection rate[a]	3.8
Responders after 5-12 months[b]	
- Complete response	42 (64.6%)
- Partial response	15 (23.1%)
- No response / study endpoint reached	8 (12.3%)

Values are number (percentage) or median (range) unless otherwise indicated. LN = lupus nephritis; ESRD = end-stage renal disease; [a]number of patients with a renal relapse or serious infection / 100 patient years; [b]no data were available for six patients; *reasons for lost to follow-up: withdrawal of informed consent; afraid of infertility (week 13), severe psychosis (week 16), protocol violation (week 27), unknown (week 38), and immigration (week 186).

Figure 1. *Flow diagram, showing the number of patients starting intravenous cyclophosphamide (ivCY) plus oral prednisone (OP) for six months, followed by mycophenolate mofetil (MMF) plus OP for 18 months, and then azathioprine (AZA) plus OP*



treatment), whereas painful joints and chubby cheeks/face occurred less frequently over time (58% and 46% after four years, $p < 0.01$). Both subscales of the IRGL (mobility and impact of disease) improved significantly over time.

DISCUSSION

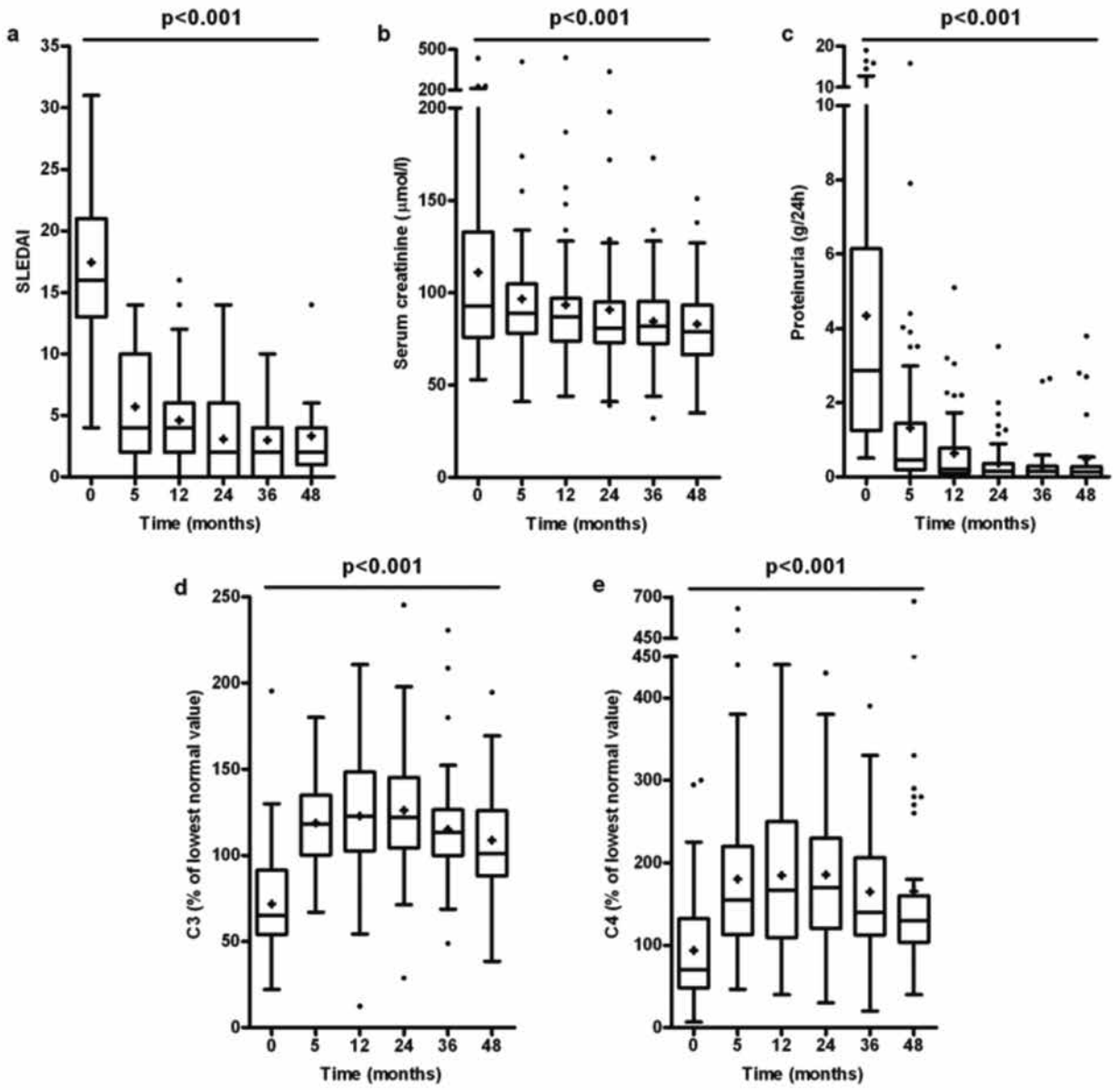
In this report, we present the 45-month follow-up data of the second Dutch Lupus Nephritis study, an open-label study evaluating the efficacy of short-term ivCY (750 mg/m^2, six pulses) followed by MMF (18 months) and azathioprine in patients with proliferative lupus nephritis. During follow-up, 5.6% of patients had a renal relapse, 1.4% reached ESRD and 2.8% died. In comparison, 4.0% had a renal flare, 0% reached ESRD and 4.0% died during the 5.5 years of follow-up of the first Dutch Lupus Nephritis study, in which patients received ivCY for 24 months (six monthly pulses, as in the present study, and thereafter every three months; in total 13 pulses) followed by azathioprine. All these endpoints were reached within four years. The occurrence of serious infections was also comparable between the two studies.[18]

In contrast, Contreras *et al.* reported that short-term ivCY (500-1000 mg/m^2, median six pulses) followed by MMF or azathioprine was more efficacious and safer than long-term ivCY (median 25 months). During 25-30 months of treatment, renal relapses (based on doubling of the urinary protein : creatinine ratio), ESRD, and mortality occurred in 40%, 10%, and 20% of the patients in the long-term CY group, respectively, compared with 15%, 5%, and 5% in the CY/MMF group and 32%, 0%, and 0% in the CY/azathioprine group.[7] It is important to note that this study included predominantly Hispanic and Black patients, while our study included mainly Caucasians.

In the last decade, several alternative treatment regimens have been evaluated. The Euro-Lupus Nephritis Trial compared high-dose (500 mg/m^2 escalating to maximum 1500 mg per pulse, eight pulses) and low-dose (fixed dose 500 mg, six pulses) ivCY followed by azathioprine. During 41 months of follow-up, 29% experienced a severe renal flare (defined as renal impairment based on > 33% increase in serum creatinine within one month, increase in proteinuria, or severe systemic disease), 4% reached ESRD, and 0% died after high-dose ivCY, while this was the case in 27%, 2% and 5%, respectively, of the patients receiving low-dose ivCY.[5] The ten-year follow-up data confirmed that low-dose ivCY followed by azathioprine is an alternative for the long-term high-dose NIH regimen.[19] The Aspreva Lupus Management Study (ALMS) demonstrated that 24 weeks of induction therapy with MMF was as effective as high-dose ivCY.[20] Subsequently, maintenance treatment with MMF was shown to be superior to azathioprine in maintaining renal response and preventing relapses. During the 36-month maintenance phase, renal relapses, ESRD, and mortality occurred in 13%, 0%, and 0%, respectively, of the patients treated with MMF and in 23%, 3%, and 1% treated with azathioprine.[21] However, one should realise that only patients with a favourable response on induction treatment were randomised at 24 weeks. Our approach of treating all patients with MMF is clinically more relevant, since not all patients will have achieved a therapeutic response at six months. The MAINTAIN Nephritis trial showed comparable efficacy of maintenance treatment with MMF and after short-term ivCY (500 mg, six pulses) combined with methylprednisolone (MP). During 48-month follow-up, renal flares occurred in 19% of the patients in the MMF group compared with 25% in the azathioprine group.[22] Therefore, in Caucasian patients, long-term treatment with azathioprine is a good option, as was also observed in our study.

Overall, the percentage of patients who reached ESRD or died during 2-4 years of follow-up was low and comparable between the different ivCY regimens and induction treatment with MMF. The results regarding the occurrence of renal relapse are difficult to compare between the

Figure 2. *Clinical and laboratory values during follow-up: (a) SLE Disease Activity Index (SLEDAI), (b) serum creatinine, (c) proteinuria, (d) complement factor 3 (C3), (e) complement factor 4 (C4)*



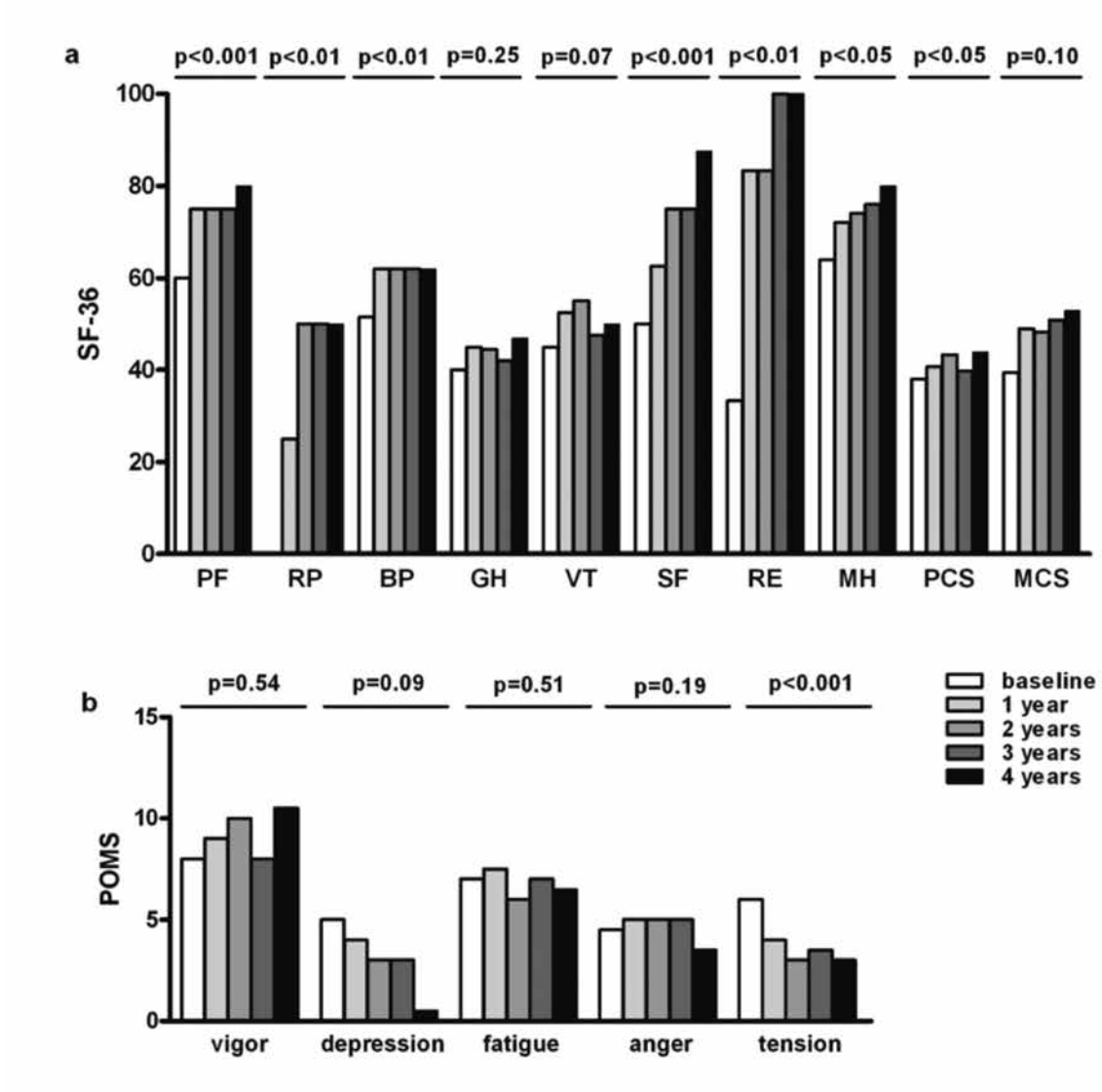
Box-and-whisker plots (Tukey): boxes indicate medians with interquartile ranges; + indicates means; whiskers indicate 1.5 times the interquartile distances; • indicates outliers. P-values represent change over time.

studies due to differences in definitions. All recently published guidelines indicate that induction therapy with ivCY or MMF along with glucocorticoids is recommended for patients with class III or IV lupus nephritis. MMF (2000-3000 mg daily for six months) is preferred over ivCY in African Americans and Hispanics as well as in patients who wish to preserve fertility. Furthermore, low-dose ivCY (500 mg every two weeks for six pulses) is preferred over high-dose ivCY (500-1000 mg/m^2 once a month for six pulses) in whites with European background.[8,23,24]

Azathioprine is not recommended as first choice for induction therapy in patients with proliferative lupus nephritis.[8,23,25] However, our previously published data regarding long-term renal function showed that induction therapy with azathioprine/MP can serve as an alternative for CY in patients with proliferative lupus nephritis who wish to avoid infertility or who have a high risk of premature ovarian failure.[26] Furthermore, azathioprine allows pregnancy in contrast to MMF.

Besides the low proportion of patients who reached the study endpoints, we found that short-term ivCY followed by

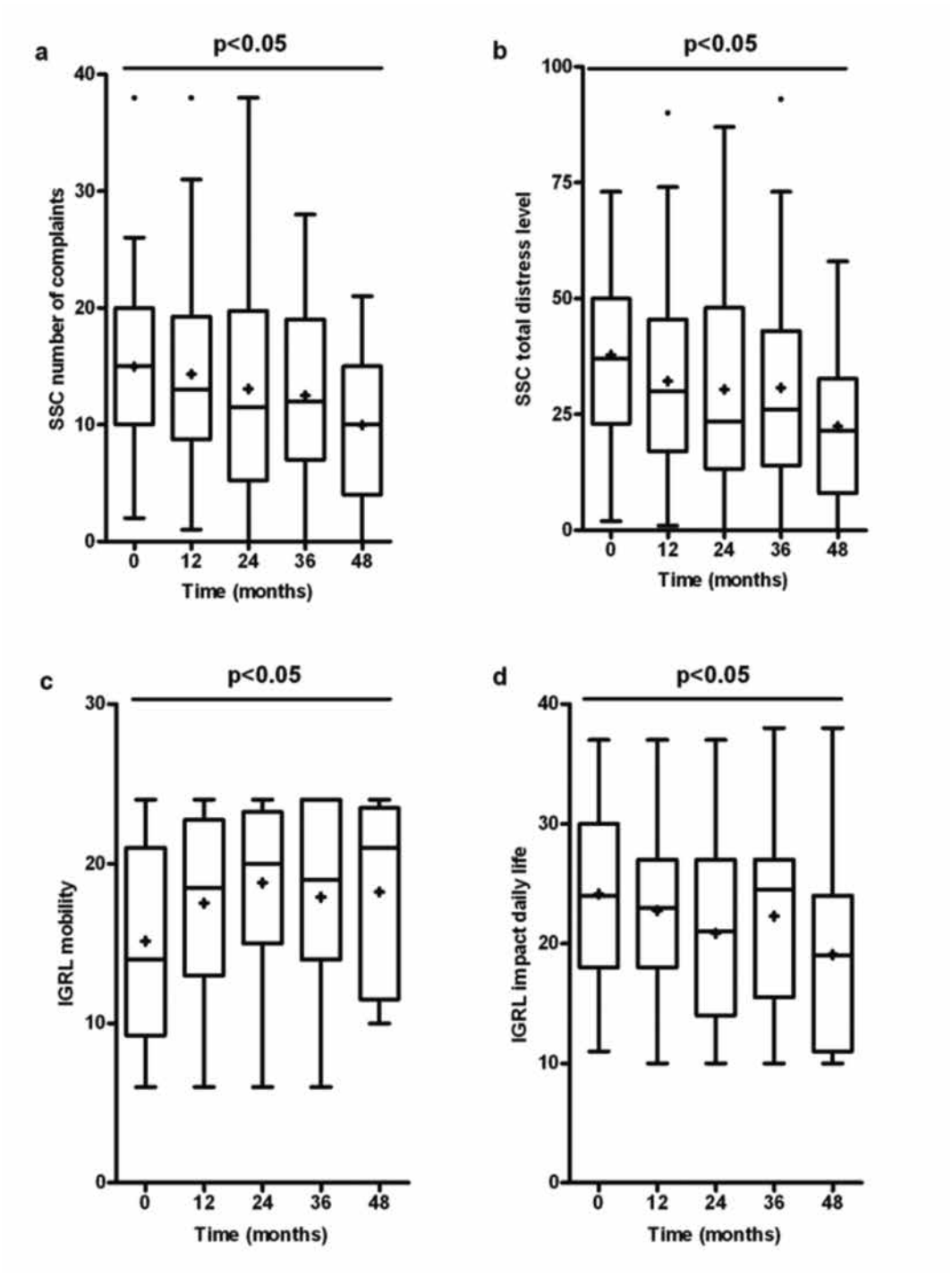
Figure 3. *Generic HRQoL during follow-up: (a) Short Form-36 Health Survey (SF-36), (b) Profile of Mood States (POMS)*



Median values are presented. P-values represent change over time. PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; PCS = physical component summary; MCS = mental component summary.

MMF resulted in significant improvements in all laboratory parameters. But what could be the place for short-term ivCY treatment followed by MMF? On the basis of the current knowledge, one could argue that short-term ivCY/MMF could be given to patients in whom MMF induction treatment fails or to patients who experience a relapse during MMF maintenance treatment. Nowadays, the use of high-dose steroids, as used in the present study, is debated. The recent rituxilup protocol showed good results without the use of oral steroids. This protocol consisted of two doses of rituximab (RTX; 1 g) and MP (500 mg) on days 1 and 15 followed by MMF maintenance treatment (initially 500 mg twice a day, titrated (to a maximum dose of 1.5 g twice a day) to 12 h trough mycophenolic acid levels of 1.2-2.4 mg/l, providing the leukocyte count and gastrointestinal symptoms allowed this).[27] The relatively high proportion of patients suffering from avascular necrosis in our study may be related to the high dose of steroids. However, one should realise that osteonecrosis is not uncommon in SLE. In a prospective MRI study, the incidence of steroid-associated osteonecrosis was 37% in the hip and knee joints of SLE patients.[28]

Figure 4. *Disease-specific HRQoL during follow-up: (a, b) SLE Symptom Checklist (SSC), (c, d) Influence of Rheumatic Diseases on General health and Lifestyle (IRGL) questionnaire*



Median values are presented. P-values represent change over time.

The Outcome Measures in Rheumatology (OMERACT) recommended that both generic and disease-specific HRQoL instruments should be included in RCTs and longitudinal observational studies in SLE.[29] In the present study, we found that short-term ivCY followed by MMF resulted in a significant improvement in most domains of the SF-36, the most commonly used generic instrument in SLE, as well as in disease-specific QoL measured by the SSC and the IRGL. In agreement with previous studies,[30-32] fatigue was the most disturbing

symptom and remained present in most patients during treatment.

Three previous studies have investigated the effect of treatment on HRQoL in patients with lupus nephritis. The first Dutch Lupus Nephritis study showed that induction treatment with long-term ivCY or azathioprine resulted in significant improvement of HRQoL. Overall, the scores at baseline as well as the improvement after treatment were comparable with those found in the present study.[31] Tse *et al.* found that HRQoL, as measured by the SF-36 and World Health Organisation QoL (WHOQoL), was higher during induction treatment with MMF compared with oral CY.[33] Recently, Daleboudt *et al.* reported that the Euro-Lupus protocol tends to result in better HRQoL, as measured by SF-36 and SSC, than the NIH protocol.[32] In these last two studies, patients were asked to fill in the questionnaires on the basis of recall about the first six months of treatment. Therefore, comparison of the HRQoL scores with those found in our study is difficult.

A limitation of this study is the relatively short follow-up time (median 3.8 years). However, two recent analyses in patient cohorts with comparable ethnic background and clinical characteristics showed that the ten-year follow-up data did not differ from those observed after four years.[19,26] An additional limitation was that the interpretation of QoL data with respect to the different phases of treatment was limited by the timing of the questionnaires. The questionnaires were sent every 12 months and related to the past months or days (depending on the questionnaire). Therefore, no information was available at six months, prohibiting an evaluation of short-term ivCY on the different domains of HRQoL.

In conclusion, this open-label study shows that induction therapy with short-term (six monthly pulses) high-dose ivCY followed by MMF is effective in preventing renal relapses, ESRD and mortality in patients with proliferative lupus nephritis. The relatively low proportion of patients reaching these study endpoints, together with the significant improvements in laboratory parameters and HRQoL, confirms that induction therapy with short-term high-dose ivCY followed by MMF can be considered in patients with proliferative lupus nephritis. In the current guidelines for treatment of proliferative lupus nephritis, treatment with low-dose ivCY or MMF is first choice. For those who do not adequately respond to induction treatment with these regimens, RTX is recommended. If RTX is unavailable, the current data suggest that high-dose ivCY followed by MMF might be an alternative.

ACKNOWLEDGEMENTS

This study was financially supported by the Eurolupus 2008 Foundation and the Dutch Kidney Foundation (C02.2005). The authors would like to thank G. Ligtenberg for the initial coordination of the study, C. van Straalen for her contribution to the data collection and all patients and physicians who participated in the second Dutch Lupus Nephritis Study: Academic Medical Centre, Amsterdam (ten Berge, de Glas-Vos, Koopman); Bronovo, The Hague (Westedt); Catharina Hospital, Eindhoven (Konings); Franciscus Hospital, Roosendaal (Noordzij); Haga Hospital, The Hague (van Buren); Jeroen Bosch Hospital, 's Hertogenbosch (Beutler, Hollander, Hoogeveen); Maasstad Hospital, Rotterdam (Boots, Kramer, Walravens); Maxima Medical Center, Eindhoven (van de Wall Bake, Verheesen); Meander Medical Center, Amersfoort (Hagen); Medical Center Leeuwarden, Leeuwarden (Halma); Reinier de Graaf, Delft (Chang, Boom); Red Cross Hospital, Beverwijk (Schrijver); Rijnstate Hospital, Arnhem (Parlevliet, Reichert); Sint Franciscus Gasthuis, Rotterdam (Wouters); University Medical Center Utrecht, Utrecht (Bijlsma, Blankenstijn, Hené, Kruize); Hospital Gelderse Vallei, Ede (Feith); Ziekenhuisgroep Twente, Almelo (Haagsma, Oostveen).

DISCLOSURES

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Eurolupus 2008 Foundation.

Data from this manuscript have been presented at the following meetings:

S. Arends, J.H. Berden, C. Grootscholten, R.H. Derksen, S.P. Berger, R.G. de Sévaux, A.E. Voskuyl, M. Bijl. Health-related quality of life in patients with proliferative lupus nephritis treated with short-term high-dose intravenous cyclophosphamide followed by mycophenolate mofetil. Poster EULAR, Madrid, 12-15 June 2013. Ann Rheum Dis 2013;72(Suppl3):262. Poster NVR Najaarsdagen, Arnhem, 26-27 September 2013.

S. Arends, J.H.M. Berden, C. Grootscholten, R.H.W.M. Derksen, S.P. Berger, R.G.L. de Sevaux, A.E. Voskuyl, M. Bijl. Induction therapy with short-term high dose intravenous cyclophosphamide followed by mycophenolate mofetil in patients with proliferative Lupus Nephritis. Oral presentation Najaarssymposium NfN, Utrecht, 7 October 2011. Poster EULAR, Berlin, 6-9 June 2012. Ann Rheum Dis 2012;71(Suppl3):540. Poster NVR Najaarsdagen, Arnhem, 27-28 September 2012.

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Netherlands
The Journal of Medicine

CASE REPORT

Reactivated Moraxella osteitis presenting as granulomatous disease

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ABSTRACT

Granulomatous infections are commonly associated with mycobacteria, brucellosis, actinomycosis, nocardiosis, spirochetes, and fungi. Rarely, granuloma formation is a host response to other bacterial infection. Osteomyelitis and osteitis that reactivate many years after the primary episode is a known phenomenon. A reactivation that presents as a granulomatous disease is rare. We present a case of reactivated osteitis due to *Moraxella osloensis* with consecutive granuloma formation.

KEYWORDS

Osteomyelitis, granulomatous disease, *Moraxella osloensis*

What was known on this topic?
Osteomyelitis that reactivates many years after the primary episode is a known phenomenon. Most reported cases are of *Staphylococcus aureus* as the causative pathogen.

What does this add?
This case is the first description of a reactivated osteitis due to *M. osloensis* triggering extensive granuloma formation. The clinical constellation may be misdiagnosed as musculoskeletal tumour or autoimmune disease. Molecular analyses may be required to identify difficult-to-detect microorganism.

INTRODUCTION

The differential diagnosis for granulomatous disorders is broad.[1] It includes infections, vasculitis, immunological aberrations, leukocyte oxidase defects, hypersensitivity reactions, host response to chemicals, or neoplasia. Granulomatous infections are commonly associated with mycobacteria, brucellosis, actinomycosis, nocardiosis, spirochetes, and fungi.[2] Rarely, granuloma formation is a host response to other bacterial infection. Granuloma formation can also be triggered by osteomyelitis and osteitis. Here, we present a case of reactivated osteitis due to *Moraxella osloensis* that presented as granulomatous disease.

CASE REPORT

A 51-year-old woman presented with a progressive and slightly painful swelling arising in the soft tissue of her left forearm. She reported neither fever, nor weight loss, nor other systemic symptoms. Her history included a forearm fracture at the site of the current swelling, 46 years ago (i.e. in her early childhood). She recalled a surgical intervention, but did not remember the type of intervention, hospitalisations, medications, or follow-ups. Magnetic resonance imaging (MRI) showed a tumour surrounding the extensor tendon group, communicating with the cortical bone of the radius (*figure 1A*). Under suspicion of a malignant or myofibroblastic tumour, an incision biopsy was performed. The histopathological analysis did not reveal any signs of malignancy but the presence of granulomas. Culture for bacteria, *Nocardia*, mycobacteria, and fungi were negative. Thus, the 8 x 2 x 1.5 cm tumour was radically excised. The histopathological analysis again showed chronic granulomatous inflammation consisting of epithelioid histiocytes and giant cells surrounded by fibrosis, but without necrosis.

Figure 1. *Fat-saturated contrast-enhanced T1-weighted magnetic resonance imaging of the left forearm. (A) Soft-tissue tumour mass surrounding the extensor tendon group and communicating with the cortical bone of the radius (arrow), shown at two different levels. (B) Contrast enhancement dorsal and ventral to the radius (arrows), indicating persistent bone inflammation. (C) Follow-up image one year after treatment, showing normal findings*

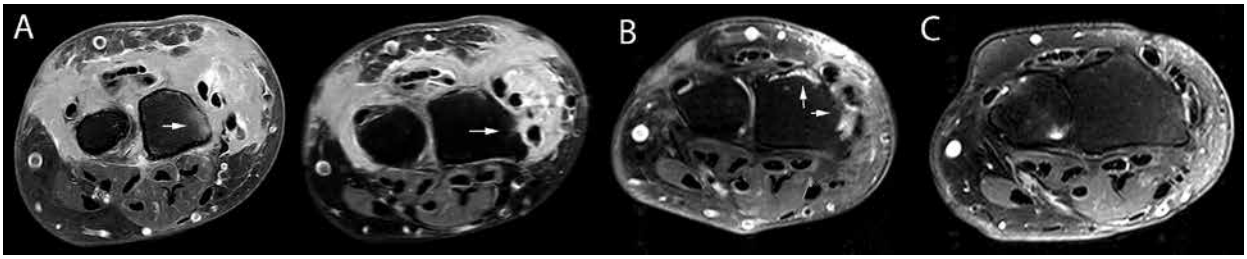
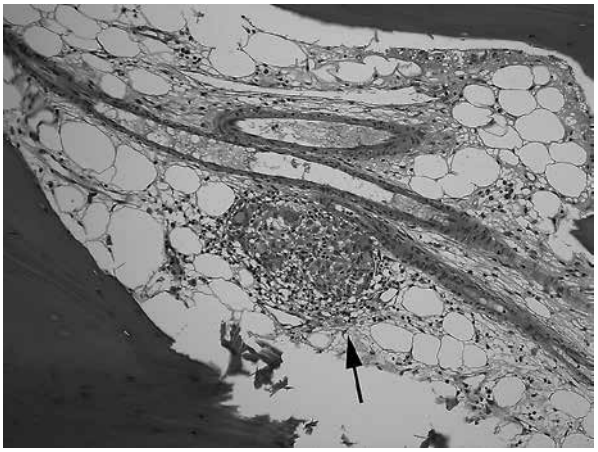


Figure 2. *Haematoxylin and eosin stain of a bone biopsy (10 x magnification) showing a granuloma in the bone marrow of the radius (arrow)*



The granulomas were also found in the cortical bone and adjacent marrow of the radius (*figure 2*).

Re-evaluation of the findings in view of a possible granulomatous disorder showed neither clinical nor laboratory signs of vasculitis (e.g. no lymphadenopathy, Wegener's, polyarteritis nodosa, systemic lupus erythematosus) or immunological aberrations (e.g. Crohn's diseases, primary biliary cirrhosis, hypogammaglobulinaemia). She denied contact with animals and chemicals. Biopsy sample cultures were negative for bacteria, *Nocardia*, mycobacteria, and fungi, as were multiple molecular analyses for mycobacteria. Serological tests for brucellosis, syphilis and Q fever were negative. The nitroblue tetrazolium dye test was not indicative of a chronic granulomatous disease. Because the finding was histopathologically consistent with an autoimmune disease (e.g. sarcoidosis), treatment with corticosteroids was initiated. After two months, the skin erythema, oedema, and warmth persisted. MRI was repeated and showed periosteal enhancement at the radius, indicative of persistent bone inflammation (*figure 1B*). When her history was re-evaluated again, the patient reported a feeling as if the disease was growing from her previous fracture site. Therefore, late reactivation of osteitis with consecutive granuloma formation was a differential diagnosis. Bone samples were reinvestigated with 16S-RNA polymerase chain reaction, revealing *Moraxella osloensis*. Corticosteroid treatment was tapered, and a three-month course with amoxicillin/clavulanate started. The further clinical course was favourable. At the one-year follow-up examination, the patient was symptom-free and MRI showed no evidence of inflammation (*figure 1C*).

DISCUSSION

Moraxella osloensis is an aerobic, gram-negative coccobacillus. Cases with bacteraemia, catheter-related infections, pneumonia, and meningitis have been reported, mostly in children or in immunocompromised hosts.[3] However, *M. osloensis* can cause osteomyelitis and arthritis.[4] In this patient, it was unclear whether the soft-tissue tumour caused bone erosions or the infection started primarily from the bone. Initially, the bone involvement was overlooked because of the impressive host reaction in the soft tissue. Also, whether or not posttraumatic bone infection occurred in her childhood remains unknown, because no disease documentation from that period was available. However, the patient's history, the sum of all radiological findings, the lack of response to corticosteroids, the identification of a pathogen from a biopsy sample and the favourable course after antimicrobial treatment suggest late reactivation of posttraumatic osteomyelitis due to *M. osloensis*.

Osteomyelitis that reactivates many years after the primary episode is a known phenomenon. Most reported cases are of *Staphylococcus aureus* as the causative pathogen. However, virtually all microorganisms can cause osteomyelitis, and conceivably, reactivate at a later stage

Table 1. *Reported cases of reactivated osteomyelitis after a long asymptomatic interval*

Reference	Gender	Location	Pathogen	Age (years)	
				1st Episode	Reactivation
5	Female	Distal femur	*S. aureus*	12	62
6	Male	Distal tibia	*Salmonella virchow*	14	26
7	Male	Distal fibula	*S. aureus*	11 and 17[1]	82
8	Male	Lumbar spondylodiscitis	*MR S. aureus*	28	40
9	Female	Calvarium	*P. acnes*	49[2]	72
10	Female	Mid-femur	*S. aureus*	10	85

This table is not exhaustive; MR = methicillin resistant; *P. acnes* = *Propionibacterium acnes*. [1]The patient had recurrent osteomyelitis in this limb as a child from the age of 11. At the age of 17, he underwent resection of the distal right fibula. Reactivated osteomyelitis occurred in the regenerated fibula. [2]Twenty-three years before presentation, the patient had undergone a craniotomy because of oligodendroglioma. No postoperative complications are described.

(*table 1*).[5-10] To the best of our knowledge, this is the first case of reactivation due to *M. osloensis*. Similar to previous cases, we were only able to identify the microorganism with 16S-RNA gene sequence analysis.[11]

Chronic granulomatous inflammation is a rare but possible host reaction to osteitis. Skouby and Knudsen presented an osteomyelits in a 3-year-old girl caused by *Kingella kingae*, formerly called *Moraxella kingie*.[12] The histopathological finding in that case was consistent with eosinophilic granuloma. In our case, the patient was 5 years old at the time of the forearm fracture, and the reactivation of osteitis occoured 46 years later.

In conclusion, this case illustrates that the extent of granuloma formation can be significantly larger than the bone infection triggering it. The patient's history pointed towards the diagnosis of reactivated osteitis. Finally, it shows that an otherwise unexplained histopathological finding of a chronic granulomatous inflammation should encourage the search for a causative pathogen, including those that are not typically associated with granulomatous infections, by all possible means.

ACKNOWLEDGEMENTS

We thank the Paediatric Haematology Laboratory of the University Children's Hospital, Bern, Switzerland, for performing the nitroblue tetrazolium dye test.

DISCLOSURES

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interest. There was no funding for this case report.

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CASE REPORT

Initially unrecognised group A streptococcal pelvic inflammatory disease in a postmenopausal woman

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ABSTRACT

Invasive group A *streptococcal* infection is a severe disease with high mortality. Invasive group A *streptococcal* infection may arise after pelvic inflammatory disease. Pelvic inflammatory disease in postmenopausal women is rare. Here, we report a unique case of a postmenopausal woman with fatal invasive group A *streptococcal* infection due to pelvic inflammatory disease and an extraordinary course of diagnosis.

KEYWORDS

Group A *streptococcus*, pelvic inflammatory disease, severe sepsis

What was known on this topic?
Invasive group A *streptococcal* infection is a severe and contagious disease. In postmenopausal women, invasive group A *streptococcal* infection due to pelvic inflammatory disease is extremely rare.

What does this add?
We describe a unique case of a postmenopausal woman with fatal group A *streptococcal* toxic shock syndrome due to pelvic inflammatory disease. This is also a cluster of fatal invasive group A *streptococcal* infection in one family.

INTRODUCTION

Streptococcal toxic shock syndrome (STSS) is a severe clinical illness characterised by shock and organ failure associated with a high mortality of up to 65%.[1] Apart from intensive medical support, STSS requires prompt recognition to enable source control and reduce toxin synthesis by the bacteria with intravenous penicillin and clindamycin.[2] In humans, the known reservoir for group A *streptococcus* (GAS) is the skin and mucous membranes. GAS causes various manifestations of acute infections including pharyngitis, tonsillitis, scarlet fever, cellulitis, erysipelas, necrotising fasciitis, and STSS. Pelvic inflammatory disease can be caused by GAS. Vaginal infection with GAS in adult women has been reported with menopausal vaginal atrophy as a prominent risk factor.[3] Currently there are no literature reports about pelvic inflammatory disease caused by GAS in postmenopausal women. We describe a case of unrecognised pelvic inflammatory disease caused by invasive GAS infection with toxic shock syndrome. The fatal occurrence of invasive GAS infection with necrotising fasciitis in a household member two weeks later became the lead to the diagnosis of the index case.

CASE REPORT

Patient A

A 72-year-old woman was admitted to hospital because of fever, abdominal pain, and diarrhoea for four days. She was on thyrax treatment for hypothyroidism. Upon presentation the patient was in shock with a heart rate of 120 beats/min and blood pressure of 70/40 mmHg. Her temperature was 37.3 °C, respiratory rate was 25

breaths/min, and oxygen saturation was immeasurable due to poor circulation. On physical examination there was diffuse abdominal pain without abdominal guarding. Her hands were blue-coloured; no other skin abnormalities were observed. Pelvic examination was not performed. Blood cultures could not be obtained because of her poor circulation. Initial vascular access was impossible and initial fluid resuscitation was achieved by the intra-osseous route. Urine analysis and culture were not taken because of anuria. Laboratory findings after initial resuscitation were: haemoglobin 8.3 mmol/l, platelets 149 x 10^9/l, white cell count 1.3 x 10^9/l, creatinine 246 µmol/l, bilirubin 38 µmol/l, aspartate aminotransferase 183 U/l, alanine aminotransferase 70 U/l, lactate dehydrogenase 461 U/l, alkaline phosphatase 54 U/l, gamma glutamyltransferase 99 U/l, creatinine kinase 5499 U/l, lactate 6.1 mmol/l, and procalcitonin > 100 ng/ml. Arterial pH was 7.19 and bicarbonate was 10 mmol/l. No abnormalities were seen on a chest X-ray. A CT scan of the abdomen showed a nonspecific swelling of the duodenum, descending and sigmoid colon and also free fluid in the pouch of Douglas. There were no signs of perforation, ischaemia or pelvic inflammatory disease. The patient was admitted to the intensive care unit (ICU) with a severe sepsis of unknown origin; antibiotic treatment included cefuroxime, metronidazole, and tobramycin. Despite treatment her condition deteriorated and she died 12 hours after admission.

Patient B

Two weeks after the death of patient A, her 82-year-old husband visited the emergency department because of excruciating pain in his right leg and shock. His medical history included diabetes mellitus and erythroderma due to cutaneous T-cell lymphoma. His medication included azathioprine, ciclosporin, and prednisone. He was diagnosed with necrotising fasciitis and after surgery he was admitted to our ICU. Blood cultures showed GAS. This patient developed multi-organ failure and died six days after admission.

Additional information

Autopsy was performed in patient A, showing signs of severe sepsis without a definite focus in the initial macroscopic report. Shortly after the death of patient B, a vaginal culture of patient A taken by the general practitioner because of vulvodynia a few days before her admission showed GAS. The final microscopic results of the post-mortem examination of patient A showed bilateral ovarian abscesses (*figure 1*) with Gram-positive cocci (*figure 2*). The isolate from the vaginal culture of patient A had not been stored and was therefore not available for genotypical comparison with the isolate from patient B.

Figure 1. *Detailed view of abscess formation with bacteria. Black arrow: abscess. Open arrow: bacteria. Haematoxylin and eosin (HE) 10 x*

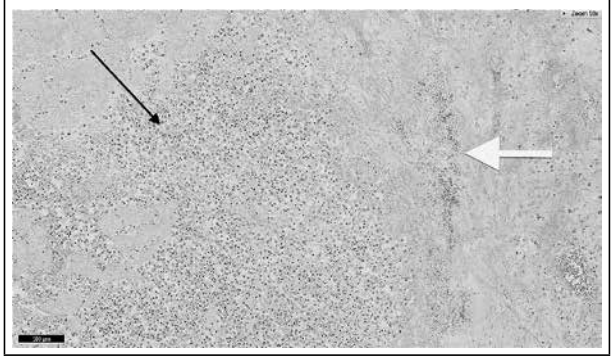
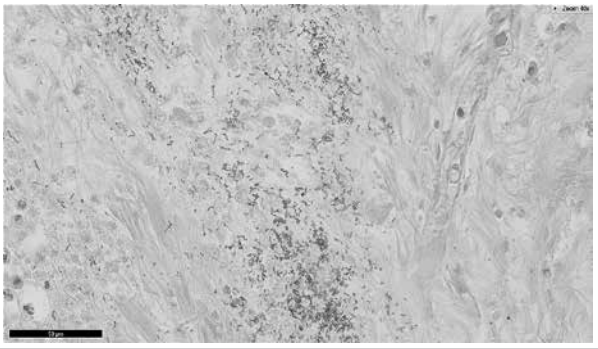


Figure 2. *Detailed view of coccoid bacteria. Haematoxylin and eosin (HE) 40 x*



DISCUSSION

This report describes two household members with fatal GAS infection. The cause of the fulminant septic shock of patient A was determined after the death of her husband, patient B. Patient A took care of the daily nursing of patient B because of his comorbidity, which may have facilitated the bacterial transfer. Although the presence of septic shock in patient A was clear, the diagnosis of toxic shock syndrome was not considered. Her history included an episode of blunt abdominal trauma due to a fall just before her fever started. Therefore, the first hypothesis was traumatic abdominal sepsis. In retrospect, the diagnosis might have been missed initially, and adequate source control may have been hampered due to several factors. Firstly, carefully reviewing the patient's history would have revealed the vulvodynia. Secondly, pelvic examination should have been performed as part of a meticulous physical examination, as this is warranted in all patients with septic shock of unknown origin. Thirdly, no blood cultures were taken, not immediately upon presentation and not after admission to the ICU.

This case report illustrates the importance of a complete medical history. If the recent history of vulvodynia had been known and the vagina culture had been examined in an affiliated laboratory, and thus noticed, we could have considered the diagnosis of STSS earlier. An extensive electronic health record would be an important solution resulting in improved communication between different organisations in our medical system.

Pelvic inflammatory disease caused by GAS in non-pregnant women is rare. A few cases about pelvic inflammatory disease and GAS infection in non-pregnant women are reported. The ages of these women ranged from 23-41 years.[4-7] There are no literature reports about postmenopausal women and pelvic inflammatory disease caused by GAS. The exact incidence of pelvic inflammatory disease in postmenopausal women is unknown; in one study less than 2% of women with tuba-ovarian abscess formation were postmenopausal.[8] Physiologically, the cervical mucus of postmenopausal women is more tenacious and serves as a mechanical barrier to ascending infections.[9] In postmenopausal women, microorganisms most frequently encountered in pelvic inflammatory disease or tuba-ovarian abscess were *E. coli* and *Klebsiella*.[8] In postmenopausal women with pelvic inflammatory disease, mortality rates of 25% have been reported despite adequate antimicrobial and surgical treatment.[10]

As we were not aware of the origin of the sepsis and its causative pathogen in patient A, her husband did not receive antibiotic prophylaxis. In the Netherlands, antibiotic prophylaxis is recommended for household members of a person with invasive GAS infection in case of necrotising fasciitis or STSS.[11] The efficacy of antibiotic prophylaxis for prevention of severe invasive GAS infection is not very well established. Although antibiotic prophylaxis is efficient in the eradication of GAS from the respiratory tract, firm evidence that antibiotic prophylaxis prevents invasive GAS infection is lacking.[12,13] However, no invasive GAS infection has been described in patients receiving antibiotic prophylaxis.[14] Risk factors for increased risk of invasive GAS infection are age exceeding 65 years, chronic cardiac and pulmonary disease, diabetes mellitus, varicella infection, human immunodeficiency virus (HIV) infection, cancer, usage of corticosteroids, injection drug use, and alcohol abuse.[15] Patient B had at least three of these risk factors.

In conclusion, we present a unique case of a postmenopausal woman with STSS due to pelvic inflammatory disease. We want to emphasise the severity of invasive GAS infection and possible difficulty in diagnosing this clinical illness. A complete medical history and meticulous physical examination is essential in postmenopausal women presenting with severe sepsis.

DISCLOSURES

This case report was written without external financial report. No conflict of interests declared.

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CASE REPORT

Increase of baclofen intoxications: risks involved and management

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ABSTRACT

Baclofen has been increasingly used in the treatment of alcohol withdrawal syndrome (AWS). We present a patient with AWS and psychiatric comorbidity who ingested 700 mg of baclofen. ICU admission was necessary for ventilatory support and symptomatic treatment. The patient was dismissed without sequelae.

KEYWORDS

Alcohol withdrawal syndrome, baclofen, intoxication, overdose, poisoning

What was known on this topic?
Baclofen is a centrally acting $GABA_B$ receptor agonist and is used in the treatment of muscle spasticity in patients suffering from spinal or cerebral disorders or from multiple sclerosis.

What does this add?
We have noticed an increased risk of baclofen intoxications, e.g. amongst users treated for substance withdrawal syndromes. Although baclofen intoxications are in most cases not fatal, respiratory support is crucial in severe intoxications. We encourage healthcare professionals to prepare themselves on the difficulties involved to diagnose a baclofen intoxication and the management of these intoxications.

INTRODUCTION

Baclofen is a centrally acting lipophilic derivative of gamma-aminobutyric acid (GABA) and acts as an agonist on the $GABA_B$ receptor.[1] Baclofen is used in the treatment of muscle spasticity in patients suffering from spinal or cerebral disorders or from multiple sclerosis,[2] and off-label it is used in the treatment of chronic hiccups.[3]
In recent years, baclofen is increasingly used in the treatment of alcohol withdrawal syndrome (AWS).[4] AWS is a cluster of symptoms that may occur after cessation or reduction in alcohol use in heavily or prolonged alcohol users.[5] Some data suggest that baclofen has comparable efficacy to the benzodiazepine diazepam and that it potentially reduces the need for benzodiazepines.[6,7]
We present a patient with AWS and psychiatric comorbidity, who self-ingested a massive amount of baclofen.

CASE REPORT

A 46-year-old female with a history of at least eight years of alcohol abuse was treated for panic disorders and alcohol abuse with baclofen 10 mg three times a day, oxazepam 10 mg daily and clomipramine 75 mg daily. The baclofen was prescribed to prevent AWS and to treat the craving for alcohol.
She was admitted to the hospital emergency ward after having ingested 700 mg of baclofen (70 tablets of 10 mg) as reported by her spouse. At admission, three hours after

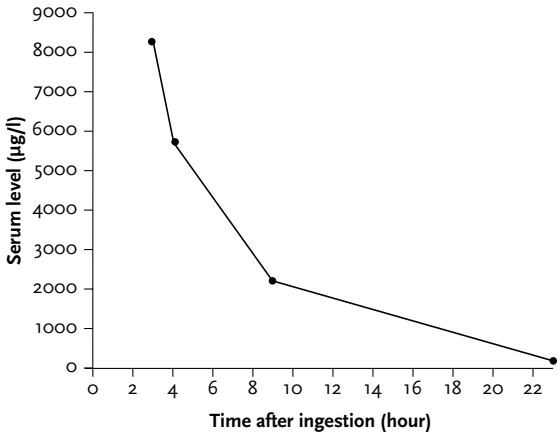
ingestion, she was restless and sweating with nausea and vomiting. She found it difficult to attain her attention and she could barely answer questions. However, she indicated that she had not consumed alcohol during the last three days. Her Glasgow Coma Scale was E4M6V4 on admission, but consciousness decreased rapidly thereafter. She had wide pupils reactive to light, hypothermia (35.4 °C) and hypertension 220/114 mmHg with a pulse of 80 beats/min. The ECG showed no abnormalities.

She was admitted to the ICU, where she was intubated and mechanically ventilated because of respiratory failure, to protect the airways for aspiration, and to perform adequate bronchial toilet. Thereafter, she was sedated with propofol via continuous infusion to facilitate the mechanical ventilation and mitigate AWS symptoms. Following intubation active charcoal and a laxative were administered through a nasogastral tube.

Besides a slight hyponatraemia and hypokalaemia, the laboratory values were normal. Serum ethanol levels were undetectable. The serum carbohydrate-deficient transferrin (N-Latex) level was in the normal range suggesting no recent excessive alcohol ingestion. The serum clomipramine level was low. Serum baclofen levels were sampled at several time points (*figure 1*). The serum baclofen level at admission was 8221 µg/l, therapeutic levels are 80-400 µg/l.[1] The level dropped to 171 µg/l 23 hours after ingestion.

During the night the restlessness persisted. Therefore propofol was only discontinued on day 2, after which she regained consciousness, and was weaned from the mechanical ventilation. She recalled that she had heard voices, after which she had ingested the baclofen. She had not taken an overdose before, and did not have an active death wish. The patient was discharged to a psychiatric hospital without sequelae from the baclofen intoxication.

Figure 1. *Serum baclofen levels after ingestion of 700 mg baclofen*



DISCUSSION

Generally, following an overdose with baclofen, effects on the central nervous system (CNS) can be observed within 2-6 hours after ingestion. Patients may become lethargic and flaccid, and experience loss of muscle strength, followed by respiratory depression, bradycardia and depressed consciousness to coma. Generalised convulsions and heart conduction disorders can also occur. Other symptoms are confusion, areflexia, hypothermia, miosis or mydriasis, sialorrhoea, hypotension, nausea, vomiting, diarrhoea, hypotonia and myoclonia.[8,9] Also transient elevations of lactic dehydrogenase, aspartate transaminase, alkaline phosphatase, white blood cell count, and glucose have been reported.[1] With an intoxication of unknown cause, it may be difficult to distinguish the symptoms caused by baclofen from many other drugs acting on the CNS. Consequently, it is important to consider the possibility of a baclofen intoxication and a specific laboratory analysis should be performed because baclofen cannot be determined with standard toxicological screening methods.

There are literature reports of prolonged baclofen intoxications that have lasted for five days in which patients were mistakenly diagnosed with brain death.[10] This prolonged effect was probably due to baclofen accumulation in the brain. First, toxic doses of baclofen may occasionally result in prolonged serum elimination half-life,[10] up to 34.5 hours,[11] compared with 3-4 hours after therapeutic doses in adults. In the present case the serum elimination half-life was within the normal range (3.6 hours). Furthermore, baclofen clearance from the brain, probably mediated by organic anion transporters, may be limited.[8,10] Therefore, one should be aware that serum concentrations may not correlate with the extent of CNS depression.

The management of baclofen intoxications is mainly symptomatic. Baclofen intoxications are not fatal in most cases, although respiratory support is crucial in severe intoxications.[2,8] There were no lethal cases reported to the Dutch National Poisons Information Centre amongst 149 baclofen intoxications in the period 2009-2011.[12] Generally, it is recommended to administer active charcoal only within one hour after baclofen ingestion.[13] Theoretically the benzodiazepine-antagonist flumazenil could counteract the binding of baclofen. However, clinical data of the efficacy of flumazenil in baclofen intoxications, and possible risks of flumazenil-induced seizures are limited.[8]

Patients with renal insufficiency have a higher risk of baclofen accumulation and toxicity, because 69-85% is eliminated unchanged by the kidney.[14] Haemodialysis can enhance baclofen elimination in cases with baclofen overdose with prolonged elimination half-life, for example due to renal failure, which is supported by its drug characteristics (e.g. low volume of distribution [0.83 l/kg in adults] and low protein binding [30%]).[14] Although some authors have performed haemodialysis in a patient with an overdose and normal kidney function,[15] generally, haemodialysis is not needed.

We have noticed an increase in published intoxications with baclofen.[2,8,10] Moreover, the Dutch National Poisons Information Centre reported an increase of baclofen-intoxicated patients from 27 in 2009, to 49 in 2010, and 73 in 2011.[12] One reason for this increase of baclofen intoxication may be the shift to intrathecal administration to treat spasticity. The therapeutic window is much smaller compared with the oral route, because of administration directly into the CNS. Secondly, there are several case reports of adolescents that are intoxicated with baclofen after using it as a recreational drug.[1,2] Although baclofen is a prescription drug, one can buy it on the internet without prescription. Finally, as described in the present case, we have noticed a rise in the use of baclofen in the treatment of AWS, and its use is also suggested for other substance withdrawal syndromes, such as with gammahydroxy butyric acid.[16] The dose of baclofen for withdrawal syndromes varies from 30 mg per day used in trials up to 270 mg per day as described in case reports.[17] There is evidence that alcohol-dependent patients frequently have comorbid psychiatric disorders.[8] These patients have a higher risk of self-intoxication or suicide.[8] Recently, a French report described a case series of 12 alcohol-dependent patients with co-existing psychiatric illness who committed a suicide attempt with baclofen, as in our case.[8]

CONCLUSION

We have noticed a rise in baclofen intoxications in recent years. The use of baclofen in substance-dependent syndromes, e.g. alcohol dependency, which is frequently accompanied by psychiatric disorders, may increase the risk of baclofen self-intoxication. Although most patients survive, ICU admission is often necessary for ventilatory support and symptomatic treatment. Healthcare professionals should be aware of the increased risks of baclofen intoxications and should prepare themselves on the management of these intoxications.

DISCLOSURES

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

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Netherlands
The Journal of Medicine

PHOTO QUIZ

A large lump in the left breast

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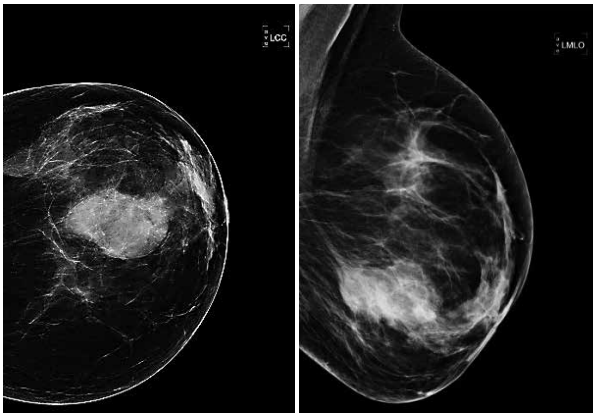
CASE REPORT

A 30-year-old woman with a history of traumatic tetraplegia was referred to our hospital with a palpable swelling of the left breast. On examination a painless swelling of the left breast and enlarged lymph nodes in the left axilla were observed. An ultrasound showed a solid inhomogenous lesion with a maximum diameter of 5.5 cm, highly suspicious of malignancy. A mammography showed similar findings (*figure 1*). A biopsy of the lesion showed no signs of malignancy, but a chronic granulomatous inflammation. Revision of biopsy material showed chronic fibrosing inflammation characterised by the presence of large amounts of histiocytes and plasma cells (*figure 2*).

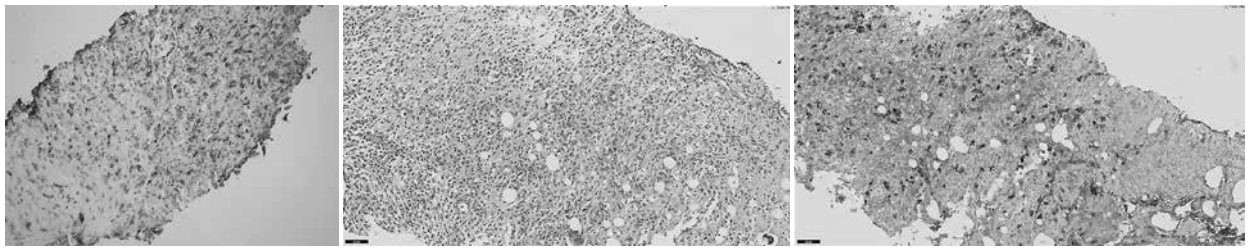
Figure 1. *Mammography shows a solid inhomogenous lesion suspicious of malignancy*



WHAT IS YOUR DIAGNOSIS?

See page 503 for the answer to this photo quiz.

Figure 2. *Biopsy of the lesion shows chronic fibrosing inflammation containing large amounts of histiocytes and plasma cells. Left: CD68 immunostaining. Middle: Haematoxylin and eosin (HE) staining; Right: IgG4 staining. 30% of the plasma cells stained positive for IgG4*



Netherlands
The Journal of Medicine

PHOTO QUIZ

A 22-year-old man with deep vein thrombosis of the left leg

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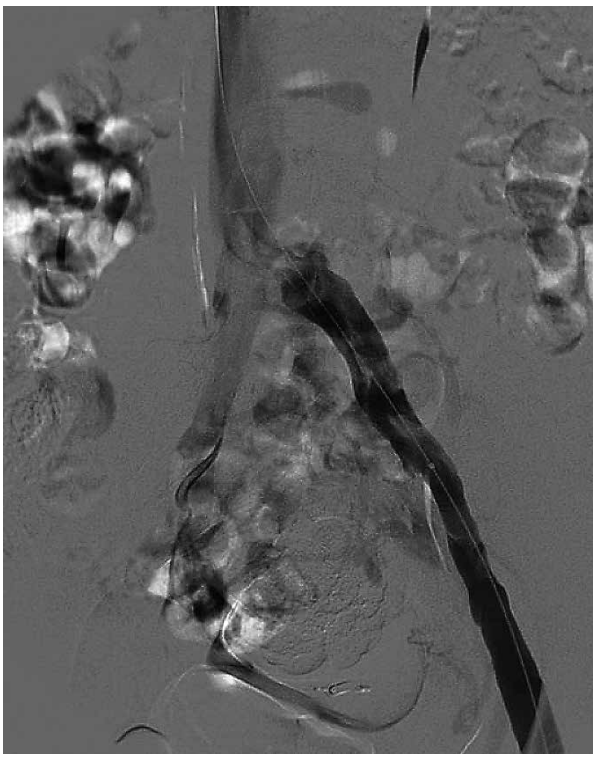
CASE REPORT

A 22-year-old man presented to our emergency department with a two-day history of progressive swelling of the left lower extremity. He denied trauma, immobilisation, dyspnoea or chest pain. The medical history was remarkable for left-sided Perthes disease. There was no medical or family history of thromboembolic disease. Physical examination revealed marked swelling and tenderness of the left leg. Duplex ultrasonography demonstrated acute deep venous thrombosis extending from the left common iliac vein down through the veins of the calf. To evaluate a potential intra-abdominal cause, computed tomography of the abdomen was performed, which showed widening of the external and common iliac veins but did not reveal the cause of the thrombosis. After initial thrombosis treatment and thrombolysis, started to prevent post-thrombotic syndrome, a venogram was performed (*figure 1*).

Figure 1. *Venogram*



WHAT IS YOUR DIAGNOSIS?

See page 504 for the answer to this photo quiz.

Netherlands
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A life-threatening complication of an ordinary urinary tract infection?

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CASE REPORT

A 42-year-old man with no medical history, besides lower back pain for eight months, was referred to our emergency department with complaints of dysarthria and confusion since one week and eight kilograms of weight loss in the last few months. On physical examination, we saw a weak and neglected patient with a blood pressure of 100/50 mmHg, heart rate of 110 beats/min and a temperature of 37.9 °C. A grade II/VI holosystolic heart murmur was heard along the right sternal border and the spleen was palpated 10 cm under the costal margin. Laboratory findings demonstrated hyponatraemia (122 mmol/l), a serum creatinine of 131 µmol/l, a raised C-reactive protein of 167 mg/l, elevated liver enzymes with cholestasis (total bilirubin 80 µmol/l), haemolytic anaemia (haemoglobin level 5.9 mmol/l, haptoglobin < 0.1 g/l), normal leukocyte count (9.0 x 10^9g/l) and thrombocytopenia (29 x 10^9g/l).

Figure 1. *Abdominal CT demonstrating splenomegaly with multiple hypodense lesions and bladder wall thickening*

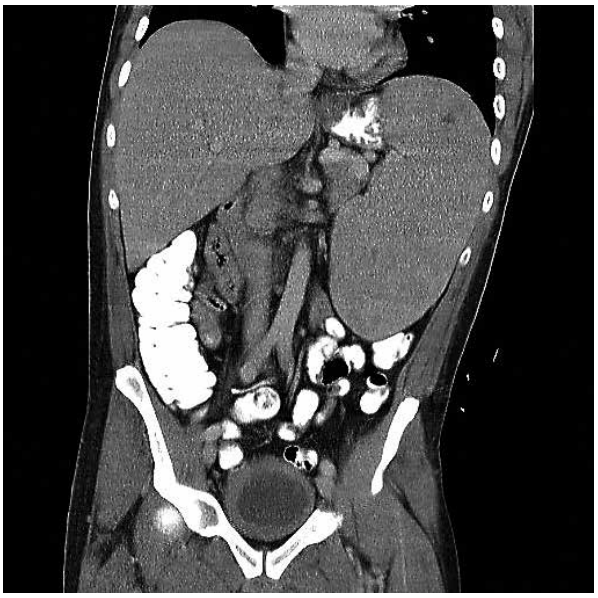
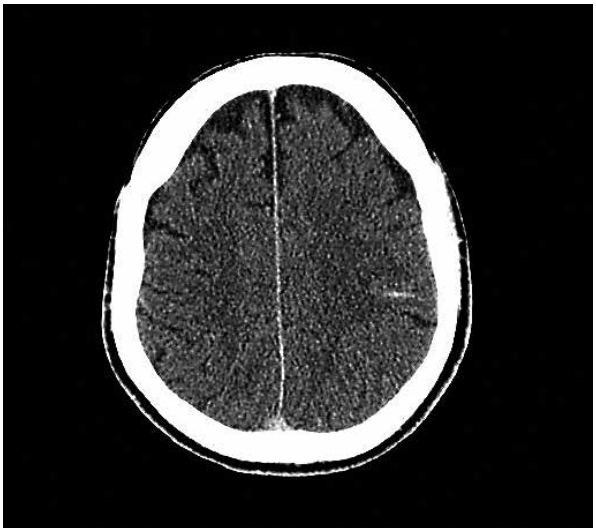


Figure 2. *Cerebral CT showing a small area of infarction in the frontal lobe*



The electrocardiography (ECG) was normal. A computed tomography (CT) scan of the abdomen was performed and showed splenomegaly with multiple hypodense lesions (*figure 1*) and thickening of the urinary bladder wall. An additional CT scan of the brain showed a small infarction in the frontal lobe (*figure 2*). Three sets of blood cultures at different times and an urine culture were taken. The patient was admitted to the intensive care unit because of haemodynamic instability. Treatment consisted of fluid resuscitation, inotropes and broad spectrum antibiotics (flucloxacillin and ceftazidime). A Gram stain of positive blood cultures showed Gram-positive cocci arranged in clusters.

WHAT IS YOUR DIAGNOSIS?

See page 505 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 500)

A LARGE LUMP IN THE LEFT BREAST

DIAGNOSIS/DISCUSSION

The patient was diagnosed with IgG4 related disease. Our differential diagnosis included a malignancy of the breast or Langerhans cell histiocytosis. There were no other signs of IgG4-related disease elsewhere.

At biopsy 30% of the plasma cells stained positive for IgG4, suggesting IgG4-related disease (IgG4-RD). Furthermore the CD68 immunostaining showed a reactive, partly histiocitic inflammatory infiltrate. Staining was negative for CD1a and S100; this excluded a Langerhans cell histiocytosis. In conclusion histology showed an infiltrate with lymphocytes, plasma cells and histiocytes. The diagnosis IgG4-related disease (IgG4-RD) was made. This was done in spite of the normal IgG4 serum levels.

IgG4-RD is a newly recognised condition of unknown aetiology, which is comprised of a collection of disorders that share specific pathological, serological and clinical features.[1] The incidence is about 2.63-10.1 patients per million people per year.[2] In 2001, autoimmune pancreatitis was related to infiltration with IgG4-positive plasma cells for the first time.[3] Furthermore, since 2003, IgG4-RD has been identified in multiple organ systems making this a systemic autoimmune condition.[1] IgG4-RD is characterised by dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, and tumour-like lesions with storiform fibrosis and destruction of the original architecture. Moreover, in more than 60% of the cases, serum IgG4 concentrations are elevated.[4] By now, IgG4-RD has been described in almost every organ system, most commonly in the pancreas and biliary tree. Regardless of the organ affected, the histopathological findings are similar.[1] The current therapy is treatment with high-dose prednisolone, based on data from several case reports.

Our patient refused treatment and a wait-and-see policy was followed. Follow-up for 18 months showed spontaneous regression of the palpable swelling in the left breast. This was confirmed by mammography.

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ANSWER TO PHOTO QUIZ (PAGE 501)

A 22-YEAR-OLD MAN WITH DEEP VEIN THROMBOSIS OF THE LEFT LEG

DIAGNOSIS

The venogram disclosed compression of the left common iliac vein, suggesting the diagnosis of May-Thurner syndrome (MTS). In 1956, May and Thurner reported the presence of focal intimal thickening with formation of septa in the left common iliac vein in 22% of autopsies.[1] MTS, or iliac vein compression syndrome, is defined as compression of the left iliac vein against the lumbar vertebrae by the overlying right common iliac artery. It has been proposed that the pulsatile artery may cause repetitive injury to the left iliac vein, resulting in progressive intimal fibrosis and development of occlusive symptoms. A review of the literature shows that MTS is most common in female patients between the ages of 20-50 years, without clear reasons for this predilection.[2]

MTS is estimated to occur in 2-5% of patients undergoing evaluation for a lower extremity venous disorder, typically presenting as a large iliofemoral deep venous thrombosis or as chronic venous insufficiency.[3] The diagnosis of MTS is made by venous duplex ultrasound and/or computed tomography or magnetic resonance imaging of the abdomen and pelvis, which can be utilised to estimate the degree of stenosis and to investigate other anatomic variations or causes of external compression on the iliac vein.

In addition to anticoagulant treatment, endovascular management is the preferred treatment for patients with deep venous thrombosis due to MTS. This treatment modality allows for catheter-directed thrombolysis and stent placement to treat mechanical entrapment and prevent post-thrombotic syndrome.[2,4,5] A study evaluating iliac vein stenting in MTS patients shows primary patency rates of 88% at 12 months and 84% at 24 months of follow-up.[6] When endovascular therapy fails, surgical management may be indicated. Iliocaval or inferior vena cava reconstruction has primary and secondary three-year patency rates of 54% and 62%.[7]

Interestingly, a recent retrospective study found that the anatomic variant defining MTS exists in a significant number of asymptomatic individuals, raising the question whether compression is the sole causal factor in symptomatic patients.[8] MTS should be considered in patients with left-sided deep venous thrombosis extending at the iliac level, which in such cases may be poorly responsive to anticoagulation alone. Although patency rates of thrombolysis and stent placement are low, anticoagulant treatment alone is unlikely to be succesful.[7]

Our patient was initially treated with subcutaneously administered tinzaparin, followed by venogram with percutaneous transluminal angioplasty and thrombolysis. After two days of urokinase treatment a stent was placed in the common iliac vein. The patient was put on lifelong oral anticoagulant treatment.

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ANSWER TO PHOTO QUIZ (PAGE 502)

A LIFE-THREATENING COMPLICATION OF AN ORDINARY URINARY TRACT INFECTION?

DIAGNOSIS

A transthoracic echocardiography showed thickening of the aortic valve cusps and a central vegetation. All blood cultures came out positive for *Aerococcus urinae*. A diagnosis of infective endocarditis due to *A. urinae*, with septic embolisation to the brain and spleen, was made. The antibiotic treatment was switched to high-dose penicillin 12 million units/day and gentamicin 3 mg/kg/day intravenously.

Infective endocarditis is a severe disease with a high mortality rate. It may be overlooked due to highly variable clinical manifestations. Early recognition of the disease and identification of the responsible pathogen are essential for starting appropriate treatment and to avert severe complications. Our patient had an unusual pathogen of infective endocarditis. Aerococci resemble staphylococci by morphology but have the biochemical and growth characteristics of streptococci and enterococci. *A. urinae* is considered to be a microorganism of low pathogenicity and is more known as a causative organism of urinary tract infections. Publications of severe and sometimes fatal infections with *A. urinae* exist, especially in the case of infective endocarditis.[1,2] Conditions predisposing patients to infections with this organism are being over the age of 65, being male and urinary tract pathology such as stricture, prostatic hyperplasia or prior surgery.[3] β-lactam antibiotics, especially penicillin, are the preferred antibiotic treatment. Adding an aminoglycoside could be beneficial in severe cases.[4] This is not very different from the antibiotics of choice for endocarditis of other aetiology. Urological evaluation of our patient, because of the bladder wall thickening and the known correlation of *A. urinae* with underlying urological conditions, revealed no such disease. Two days after the diagnosis the patient underwent surgical aortic valve replacement. Penicillin was continued for six weeks. The patient made a full recovery.

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