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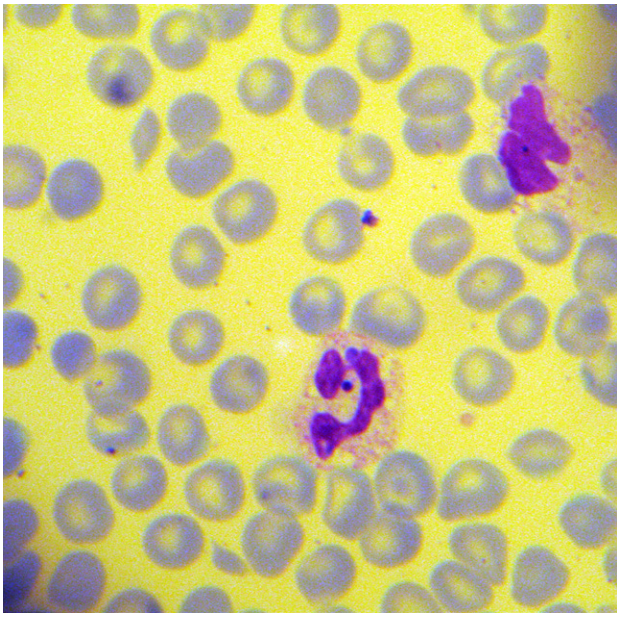

An abnormal blood smear; what is your diagnosis?

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EDITORIAL

Hitting the right target: Diagnosing undiagnosed HIV patients in the Netherlands

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In the post-2014 era of the HIV epidemic, the Joint United Nations Program on HIV/AIDS (UNAIDS) has set the 90-90-90 target with the ambitious goal of ending the AIDS epidemic by 2030.[1] The aim is that by 2020, 90% of people who are HIV infected will be diagnosed, 90% of those who are diagnosed will be receiving antiretroviral treatment (ART), and 90% of those on ART will be virally suppressed. Once undetectable, forward transmission stops. Nonetheless, in the Netherlands, fewer than 90% of HIV-infected patients knew their status by the end of 2015.[2] Comparable with other Western countries, the HIV epidemic in the Netherlands is concentrated in key populations such as men who have sex with men and individuals from HIV-endemic countries.[2] Successful interventions have mainly targeted pregnant women and gay men. Implementing effective strategies focusing on migrant populations proves to be harder, not in the least due to stigma. However, also outside these key populations, a considerable number of HIV-infected people remain undiagnosed.

How can we best trace those individuals, both inside and outside key populations, who are unaware of their status? In this issue of the Netherlands Journal of Medicine, Luiken and colleagues present a cross-sectional study in which they investigated the effect of non-targeted HIV testing at emergency departments in Amsterdam and Rotterdam.[3] If anywhere, undiagnosed individuals are among the people living in these known hot spots of the Dutch HIV epidemic. In their study, Luiken et al. intended to approach over 7500 patients regardless of their reasons for visiting, and found only two new HIV diagnoses. Importantly, both of these two heterosexual male migrants already had clues in their histories suggestive of HIV. The characteristics of the non-participating patients remain unknown, but the study also reports insightful results regarding anonymously tested patients in this group. This did not result in a single positive test. With this low yield of newly diagnosed HIV infections, non-targeted HIV testing at Dutch emergency departments was not considered cost-effective.

Evidently, every new HIV diagnosis is one that counts. Yet the observed rate is strikingly low considering the known prevalence in the participating cities. The inclusion of a relatively low number of persons from high-risk groups partly accounted for this. This fact in turn helps to calibrate interventions to reach the 90-90-90 target. The results suggest that we can identify people at risk for HIV, even outside known key populations and at emergency departments. This also corresponds with national and European guidelines that recommend HIV testing in individuals presenting to any healthcare setting with risk factors known as HIV indicator conditions.[4-6]

Two factors are vital to perform successful targeted screening: first, to identify people at risk both inside and outside key populations by recognising HIV indicator conditions, and second, to use the right diagnostic tests. To start with the first, HIV indicator conditions should always trigger HIV testing regardless of a patient's background. HIV indicator conditions are generally associated with an HIV prevalence of at least 0.1%.[6] HIV testing is cost-effective above this prevalence threshold.[6-9] They can indicate advanced HIV infection associated with decreased cellular immunity which include obvious cases such as tuberculosis, but also involve patients presenting with herpes zoster, seborrhoeic eczema or atypical psoriasis. Unfortunately, even in the case of well-established HIV indicator conditions, the testing frequency remains low.[10] It is important to consider that population-wide screening of patients with these HIV indicator conditions is clearly cost-effective, despite the fact that the majority of tests ordered by an individual clinician will be negative.[8,9] Mononucleosis-like illness associated with acute retroviral syndrome during primary HIV infection (PHI) is also regarded as an HIV indicator condition. In a large European-wide study, the HIV prevalence in individuals presenting with a mononucleosis-like illness approaches 4%.[6] Diagnosing HIV during PHI provides an important opportunity for counselling and ART initiation, and can interrupt

forward HIV transmission early as well as prevent future HIV indicator conditions associated with advanced HIV infection. In recent years, research stressing the importance of early diagnosis and immediate treatment of PHI has accumulated.[11-14] Cases have been reported where immediate treatment of PHI likely helped to control HIV after subsequent ART interruption.[15] While an estimated 50 to 90% of patients with a recently acquired HIV experience an acute retroviral syndrome and frequently contact healthcare facilities, the diagnosis is often not considered.[16,17] At present, algorithms to diagnose PHI in specific risk groups are being developed.[18] Second, regarding diagnostics, an ELISA Combotest is suitable to test patients who are suspected of having advanced HIV infection because of associated HIV indicator conditions. When PHI is considered, patients can benefit from screening with newer PCR techniques instead of ELISA to decrease false-negative results,[19,20] a testing strategy that was not, however, used in the present study.

Unfortunately, despite adequate testing facilities, testing based on clinical symptoms suggestive of PHI or a more progressed HIV infection remains difficult.[10,17,21,22] Clinicians should be aware of the possibility of HIV in those patients presenting with HIV indicator conditions, especially if they are from high-risk groups including gay men, heterosexual individuals with multiple sex partners, and migrants from HIV-endemic areas. This warrants targeted, pro-active, and repeated HIV testing by clinicians. Moreover, strategies such as self-testing and online algorithms suggesting an HIV test upon indication could prove useful to expand coverage. An ongoing Dutch initiative in this field is the HIV Transmission Elimination AMsterdam (H-Team) which includes the Netherlands Cohort Study on Acute HIV Infection (NOVA), focusing on PHI.[23] Key populations are increasingly reached by these efforts. In Dutch emergency departments, the implementation of a simple screening algorithm could help identify those at risk for HIV infection, and could also help to target those who are currently not reached within key populations or who do not belong to known key populations.

Currently, the 90% target is not reached in the Netherlands. In line with the suggestion by Luiken et al. targeted HIV testing based on risk factors is an alternative approach to decrease the number of undiagnosed people living with HIV in all populations. Awareness among clinicians of HIV indicator conditions and PHI, and subsequent adequate and repeated HIV testing merit our attention. HIV detection is a joint effort by clinicians across disciplines. If together we can improve the cascade of HIV care, a 90-90-90 future lies ahead.

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REVIEW

Cellulitis: current insights into pathophysiology and clinical management

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ABSTRACT

Cellulitis is a bacterial skin and soft tissue infection which occurs when the physical skin barrier, the immune system and/or the circulatory system are impaired. Diabetes, obesity and old age are associated with defects in all of these areas and as a result are major predisposing factors for cellulitis. In this review, we summarise current insights into the pathophysiology of cellulitis and place the Dutch guidelines on the clinical management of cellulitis of the lower extremities in perspective. Recent evidence on diagnostic strategies is discussed, the importance of which is underscored by findings that venous insufficiency, eczema, deep vein thrombosis and gout are frequently mistaken for cellulitis. Empiric antibiotic choices are designed against the background of a low prevalence of multi-resistant *Staphylococcus aureus*. Novel antimicrobial agents registered for cellulitis are also discussed. Relapses occur frequently due to a high prevalence of risk factors associated with cellulitis in combination with the occurrence of persistent post-inflammatory lymphatic damage. Lastly, we identify knowledge gaps which, if addressed, will advance our understanding of the pathophysiology of cellulitis and improve its clinical management.

KEYWORDS

Cellulitis, clinical management, pathophysiology, review

INTRODUCTION

Cellulitis (Latin: *cellula* (diminutive of *cella*: cell) + *itis* (suffix denoting inflammation)) and its subtype erysipelas (Greek: *erythrós* (red) + *pella* (skin)), are among the most frequent infections requiring hospitalisation.[1] The historical distinction between cellulitis and erysipelas, based on different bacterial aetiologies and thus treatment options, is becoming obsolete as increasing evidence suggests a large overlap between these two entities (*textbox 1*). In the Netherlands, the annual incidence is estimated to be 22 per 1000 inhabitants. Approximately 7% of all patients with cellulitis are hospitalised.[5,6] The mortality rate of hospitalised patients has been reported to be around 2.5%.[7] Recent epidemiology data on cellulitis in the Netherlands are lacking, but given the rise in the incidence of important risk factors (namely diabetes, obesity and old age), an increase in the incidence of cellulitis is expected.[8-10] Dutch guidelines on the clinical management of cellulitis of the lower extremities have been available since 2013 (*figure 1*).[11] Since their publication, numerous studies have provided novel insights and new antibiotics registered for skin and soft tissue infections have entered the market. This review discusses the current state of evidence regarding pathogenesis, diagnostics, and treatment of cellulitis. The literature search strategy used is documented in *textbox 2*.

Cellulitis: a diagnostic challenge

All that is red is not cellulitis. The classical symptoms of erythema, oedema, warmth and tenderness, are non-specific and vary in severity. The clinical presentation of cellulitis is mimicked by a whole range of diseases (*table 1* and *figure 2*). One recent study revealed that 31% of patients hospitalised with cellulitis were misdiagnosed, the most frequent mimickers being stasis dermatitis, stasis ulcers, gout, congestive heart failure, non-specific oedema and deep venous thrombosis (DVT).[18] Another study in the primary care setting found a similar rate of misdiagnoses.[19] Furthermore, when clinicians specifically consulted dermatologists because of uncertainty about a diagnosis of cellulitis, 74% of the patients turned out not

Textbox 1. *Erysipelas vs cellulitis*

Historically, physicians distinguish erysipelas, a streptococcal infection of the superficial dermis and superficially located lymphatic vessels, from cellulitis, an infection of all skin layers generally caused by staphylococci. Erysipelas is characterised by sharp demarcation, a palpable edge and salmon-red erythema and is accompanied by high fever.[2] This distinction has therapeutic implications, as beta-lactamase sensitive penicillins would suffice for erysipelas.

Aetiological evidence, however, contests the concept that erysipelas is solely caused by streptococci. For instance, a systematic review of bacteraemias in erysipelas and cellulitis patients found equal rates of *S. aureus* (14%) in both groups.[3] In addition, in a retrospective study of 1142 patients with erysipelas more than half of the positive wound cultures yielded *S. aureus*.[2] Lastly, streptococci were not found more frequently in patients with all classical erysipelas symptoms than in the general cellulitis population (68%), in a prospective aetiological study.[4]

In addition to being hard to distinguish from cellulitis based on clinical symptoms, the above suggests that diagnosing erysipelas does not help to differentiate between streptococcal and staphylococcal infections. In most studies the two conditions are already grouped together and US guidelines use the term 'skin and soft tissue infections', making management decisions based on the presence of purulence instead.[13]

Textbox 2. *Search strategy*

A systematic literature search was performed using the following keywords: (cellulitis[tiab] OR erysipelas[tiab] OR 'skin and skin structure infection'[tiab] OR 'skin and soft tissue infection'[tiab]) AND ((pathogenesis OR etiological OR risk OR precipitating OR predisposing OR pathophysiology OR microbiota) OR (ultraso* OR MRI OR 'magnetic resonance' OR tomography OR CT OR diagnostics OR serology OR serological OR culture OR cultures OR PCR OR microbiota) OR (((duration OR length) AND therapy) OR ((duration OR length) AND treatment) OR ((duration OR length) AND antibiotics) OR flucloxacillin OR dicloxacillin OR clindamycin OR ((therapy OR treatment) AND cessation OR stop OR end)) OR (toxin OR toxins) OR (criteria OR severity OR adjunctive OR prednis* OR pain OR analgesi*) OR (compression OR compressive OR compressing OR stocking OR stockings OR ACT) OR (lymphedema OR lymphatic AND (drain* OR massage)) OR (corticoster* OR steroids OR anti-inflammat* OR grade OR grades OR grading) OR (relapsing OR recurring OR recurrent OR prophylaxis OR prophylactic)) NOT periorbital[ti] NOT postseptal[ti]. Animal and paediatric studies were excluded. Guidelines, statistical sources, previous reviews and bibliographies of relevant studies were also searched for other relevant studies or information. Only studies contributing to the understanding of cellulitis were selected.

to have cellulitis.[20] Misdiagnosis results in unnecessary admissions and extra costs for perceived refractory cellulitis.[18] Leucocytosis and elevated C-reactive protein (CRP) levels are present in 34-50% and 77-97% of patients, respectively.[21,22]

Stasis dermatitis can mimic all symptoms, including mild leucocytosis and/or CRP elevation. Its origin lies in chronic venous insufficiency, which causes proliferation and increased permeability of dermal capillaries. Leucocytes migrate, cause inflammation, stimulate collagen production, and thus induce dermal fibrosis.[23] Erythrocyte extravasation causes brown skin pigmentation.[24] Untreated, stasis dermatitis can progress to lipodermatosclerosis, which is characterised by a fibrotic tightening and sometimes ulceration of the skin above the ankles. Compression therapy can correct haemodynamic effects and cytokine levels.[13]

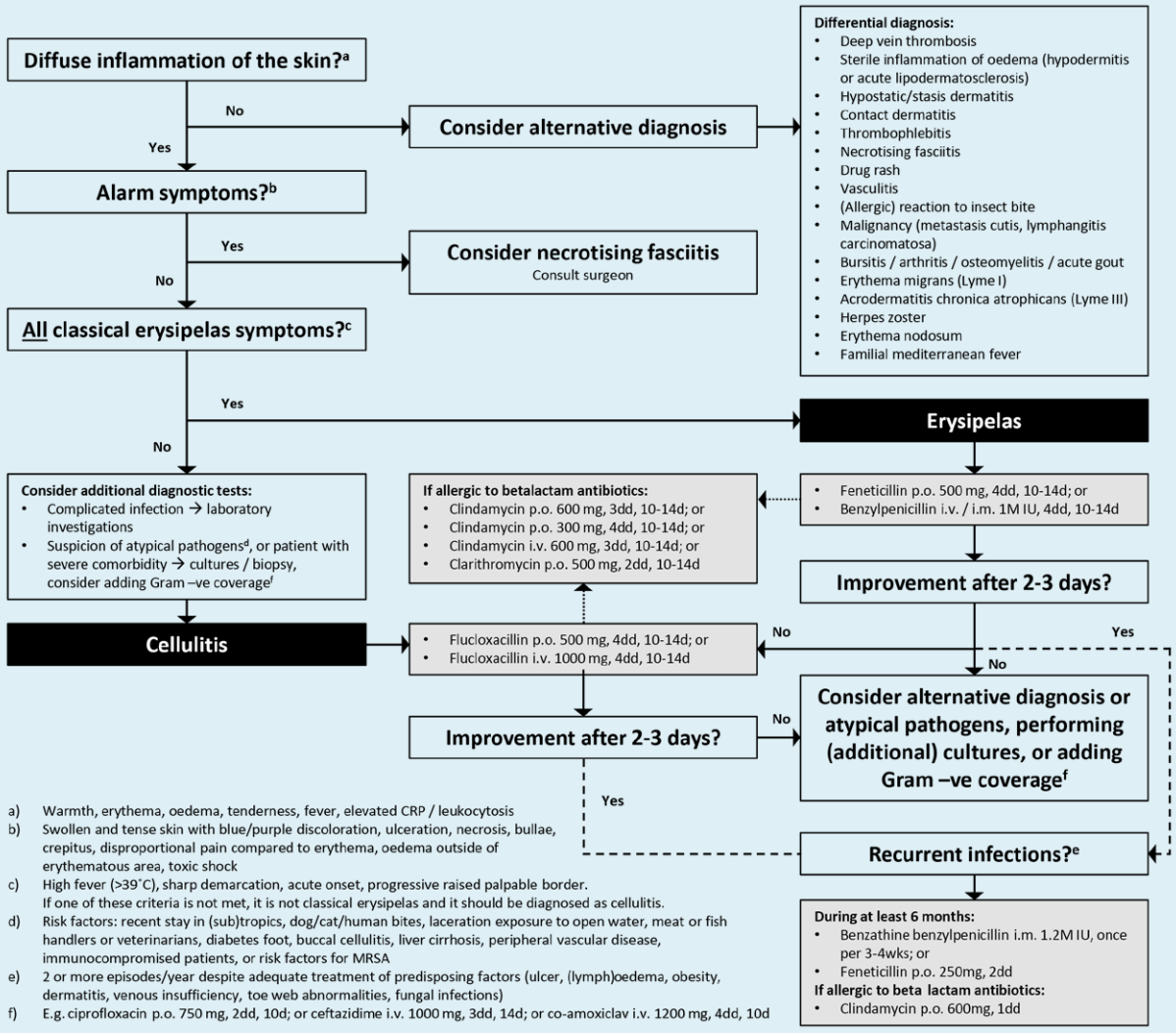
Imaging is sometimes indicated. As DVT does not occur more often in patients with cellulitis than those without, routine DVT screening is not recommended.[25] When ultrasound was only utilised among uncertain 'DVT vs cellulitis' diagnoses, 17% turned out to have DVT.[26] Ultrasound may detect occult abscesses, or disprove 'abscesses' mistakenly diagnosed during physical examination.[27] Computed tomography is not warranted due to nonspecific findings.[28] Magnetic resonance imaging and the Laboratory Risk Indicator for Necrotising Fasciitis score might help distinguish between necrotising fasciitis and cellulitis, but as yet neither have proven superior to clinical suspicion and subsequent surgical exploration.[29]

Uncomplicated superficial abscesses with erythema can be difficult to distinguish from primary cellulitis with secondary abscesses.[30] Uncomplicated abscesses are treated with incision and drainage,[31] but two recent trials show cure rate increases from 69-74% to 81-83% with adjunctive antibiotics.[32,33]

Risk factors

Multiple physical barriers and active protective mechanisms prevent the invasion of skin commensals and thus the occurrence of infection (*figure 3a*). An intact vasculature will help maintain the integrity and function

Figure 1. *Management flowchart of cellulitis and erysipelas, adapted from the Dutch 2013 guidelines*[11]



of all these barriers and mechanisms. Deficiencies in skin integrity, immunity or vasculature can be considered risk factors for the development of cellulitis (*figure 3b*). Old age, diabetes and obesity cause defects in all three of these areas, and thus confer a relatively high risk. This combination of risk factors is often seen in patients with cellulitis who are hospitalised. The biggest risk factor, however, is a positive history for cellulitis.[34]

Old age comes with skin atrophy, poor circulation, immunosenescence, and comorbidities such as diabetes or congestive heart failure. Malnourishment causes impaired wound healing, decreased skin elasticity and integrity, and relative immunosuppression.[35] Incidence, complication (e.g. bacteraemia, osteomyelitis, endocarditis) and hospitalisation rates are all higher in diabetic patients.[53] Most cases of cellulitis in diabetic patients will be attributable to diabetic foot associated skin defects, but more than a quarter of the cases of culture-positive diabetic cellulitis occur on non-foot locations.[54] In morbid obesity, the skin is more susceptible to damage and takes longer to repair.[36]

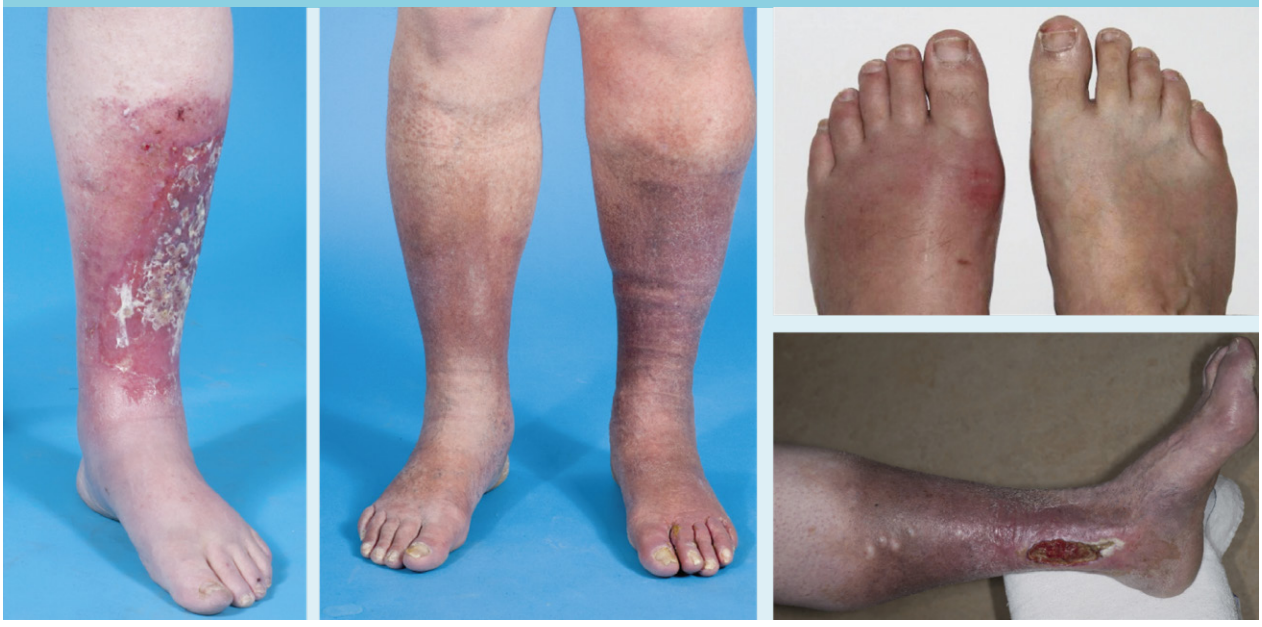
Some seasonal variability has been observed. Streptococcal skin infections occur more frequently in the winter in cold countries,[55,56] while warmer regions see a higher erysipelas incidence during the summer.[37]

Skin microbiome alterations have been observed in diseases such as atopic dermatitis, where more staphylococci and fewer streptococci are present, but also in acne.[57] *S. aureus* is shown to be overrepresented in the peri-abscess skin microbiome.[58] Pioneering studies have revealed that commensals can influence the composition of the local microbiome and alter local immunity,[59] but future studies will have to reveal relationships between the microbiome and cellulitis.

Table 1. *Mimickers of cellulitis and how to recognise them*

Mimicker	Signs suggestive for this diagnosis
Stasis dermatitis[12]	Bilateral nature (is extremely rare for cellulitis), slow onset of symptoms, hyperpigmentation, superficial desquamation
Lipodermatosclerosis[12]	Acute: pain above the medial malleolus Chronic: Inverted champagne bottle effect (leg diameter narrows below the calf), history of venous insufficiency, bronze-brown skin
Stasis ulcers[13]	Ulcer in patient with long history of chronic venous insufficiency
Gout[14]	Focal swelling and erythema limited to joints (e.g. knee or first metatarsalphalangeal joint), history of gout, tophi, increase in serum uric acid
Deep venous thrombosis[15]	History of immobilisation or cancer, thrombosis on duplex scan; no fever
Ecthyma[16]	Shallow ulcer with punched-out borders and adjacent erythema
Erysipeloid[16]	Red hands, people who work with animals
Impetigo[16]	Crusted blisters, brown-yellow scabs erosions and erythema, mostly in children
Lyme disease[16]	Painless spreading sharply demarcated erythema with central pallor (erythema migrans)
Eosinophilic cellulitis[12]	Eosinophilia, indurated plaques, itching and burning before plaque formation
Contact dermatitis[12]	Erythema confined to areas in contact with irritant (soaps, detergents, hobby materials, etc.)
Necrotising fasciitis[17]	Pain disproportionate to clinical findings and outside of lesion margins, rapid onset, systemic toxicity, bullae, purple or blue discoloration of the skin, cutaneous crepitations

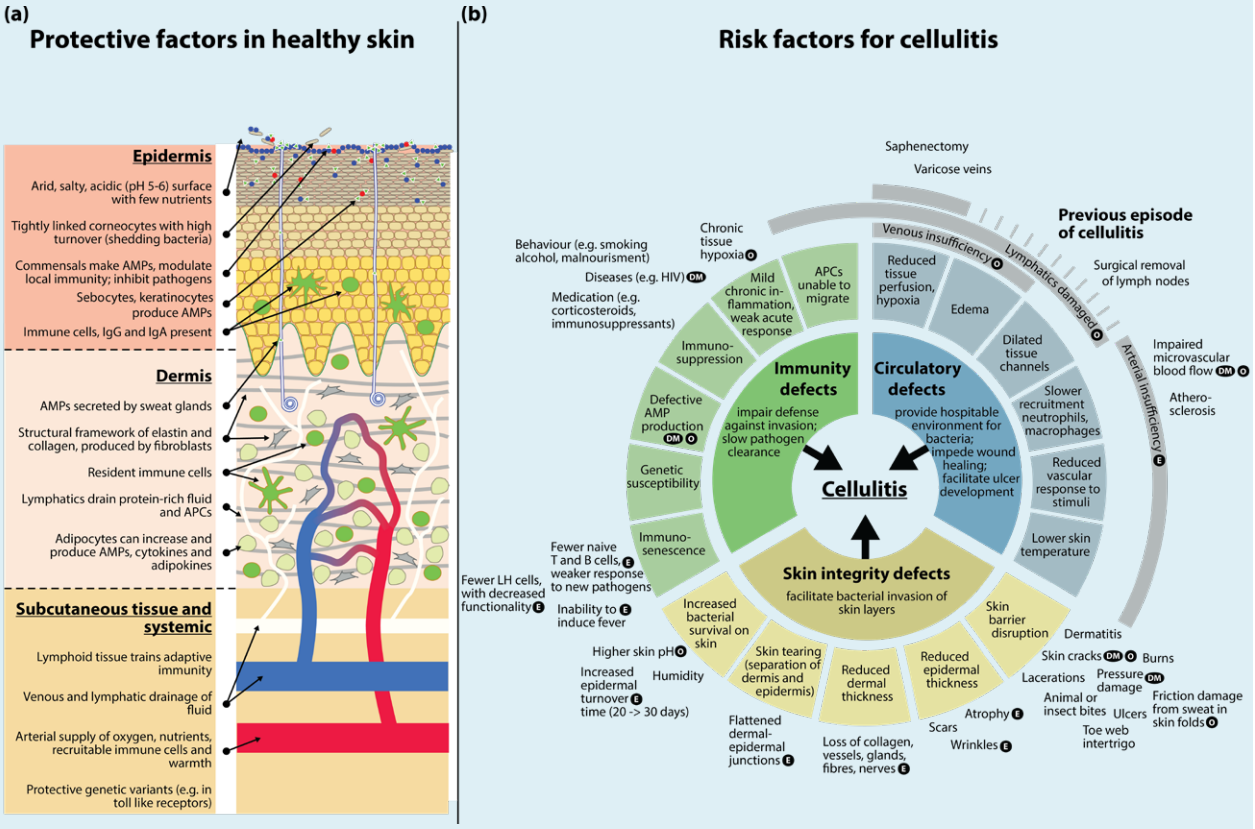
Figure 2. *Mimickers of cellulitis. Left: inflamed lower leg due to stasis dermatitis with secondary impetiginisation. Centre: hyperpigmentation due to venous insufficiency. Top right: erythema and swelling of left forefoot due to gout of first metatarsophalangeal joint (podagra). Lower right: chronic venous ulceration and tightened ankle due to lipodermatosclerosis. Top right image licensed under Creative Commons Attribution 3.0 Germany license, author 'Gonzosft', other images courtesy of Dr. A.P.M. Lavrijsen*



To admit, or not to admit

The 7% of patients who are hospitalised cause 83% of the total healthcare expenditure associated with cellulitis.[6] Unfortunately, as yet there are no validated, prospectively evaluated admission guidelines. One system distinguishes classes with supposedly increasing mortality and therapy failure rates based on systemic symptoms, comorbidity and the Standardised Early Warning Scores.[60,61] Two cohort studies compared this system with current clinical practice: one retrospectively, one prospectively.[62,63]

Figure 3. *An aetiological approach to factors protecting against (a) or predisposing for (b) cellulitis*



Factors associated with elderly (E), diabetic (DM) or obese (O) patients are marked with black circles. AMPs = antimicrobial peptides; IgG = immunoglobulin G; IgA = immunoglobulin A; APCs = antigen presenting cells; HIV = human immunodeficiency virus; LH = Langerhans.[34-52]

Overtreatment of infections that the system classified as mild (class I and II) was very common, while most of the severest infections (class IV) were undertreated. In one of the two studies, only 5 of 6 (83%) class IV patients had achieved complete resolution of symptoms at the end of therapy, compared with 100%, 98% and 96% in classes I-III.[62,63] One explanation for this is that factors not incorporated in this system currently have a substantial effect on admission and treatment practices.

Pragmatically, one could consider admission for patients with (1) poor disease perception, (2) intake problems, (3) an altered mental status, or (4) disease progression despite adequately dosed oral antibiotics. Severity or dysregulation of comorbidity (e.g. diabetes, immunodeficiency, obesity, or cardiac, renal or venous insufficiencies) and severity of infection (e.g. systemic symptoms, organ failure) should also be taken into account.[11,64]

Factors predicting oral therapy failure may also be indications for admission for intravenous antibiotics. Retrospectively identified factors associated with failure of oral antibiotic therapy include fever, chronic leg ulcers, chronic oedema and lymphoedema, prior cellulitis in the same area, and wound infections.[65,66] Additionally, after treatment in an observation unit for 24 hours, patients with cellulitis of the hand, an elevated lactate, fever, history thereof, or multiple comorbidities were more likely to be admitted.[67,68] However, this mainly reflects clinical practice rather than need for admission.

Alternatively, outpatient parenteral antibiotic therapy, where intravenous antibiotics are given at home or on outpatient basis, can avoid or shorten hospitalisation for selected patients and is usually preferred by patients.[69]

Antibiotic treatment

One might wonder if a proportion of cases of cellulitis are self-limiting and do not require antimicrobial agents. It is noteworthy that in clinical trials performed in the pre-antibiotic era, in which the effects of horse serum and ultraviolet light were evaluated, cure rates of 70% were observed.[70] On the other hand, it has also been demonstrated that inadequate empirical antibiotics are associated with prolonged treatment durations and length of hospital stay.[71] Current treatment recommendations are summarised in *figure 1*.

Streptococci and *S. aureus* are the most common pathogens identified in patients with cellulitis (*table 2*), and accumulating evidence from prospective convalescent serology studies suggests that > 70% are caused by

Table 2. *Causative agent of cellulitis depending on culture methodology*

Culture method	Cultured/total patients, % positive cultures	Pathogen distribution	Factors which increase yield	Notes
Blood culture	2731/unknown, 4% (+3% contamination)[3]* 555/1142, 9% (+2%)[2] 250/476, 4.8% (+1,6%)[72]	GAS: 24-26% OS: 37-58% SA: 8-25% GNB: 0-23%	Increased blood volume cultured, extensive infection, high CRP, fever, diabetes, chronic ulcer, alcoholism, impaired immunity, immersion injuries, animal bites.[72] Age >65, non-lower extremity involvement, cirrhosis, systemic inflammatory response syndrome[73]	Unknown if patients with Gram-negative bacteraemia had risk factors.[3] Blood cultures rarely elicit change of antibiotic class[74]
(Wound) swab culture	343/1142, 72%[2] 127/216, 75%[4]	GAS: 21-23% OS: 26-39% SA: 62-74% GNB: 10-12%	Debridement and irrigation of wound before swabbing, to avoid culturing colonisers[75]	Role of *S. aureus* and Gram negatives unknown (coloniser vs pathogen), as BHS aetiology was often confirmed or probable despite *S. aureus* growth in cultures[4]
Punch biopsy / needle aspiration culture	541/808, 24%[76]*	GAS: 27% OS: 11% SA: 51% Others: 17%	Take from point of maximum inflammation, not leading edge[77]	
Combination of wound culture, blood culture and/or serology	432/465, 48% (83% of purulent infections, 36% of non-purulent)[78]	BHS: 46% (5% purulent, 70% non-purulent) SA: 30% (60%, 12%) GNB: 11% (13%, 10%) Polymicrobial: 10% (19%, 5%)		

*Systematic review; GAS = group A streptococci; OS = other streptococci; SA = *Staphylococcus aureus*; GNB = gram-negative bacteria; BHS = beta-haemolytic streptococci.

streptococci.[4,79] Atypical pathogens can be observed in patients with selected conditions (*table 3*). In contrast to diabetic foot infections, diabetic non-foot infections are generally not caused by atypical pathogens.[87] In the Netherlands, the preferred small spectrum agent covering both methicillin-susceptible *S. aureus* and beta-haemolytic streptococci is flucloxacillin. Confirmed streptococcal infections can be treated with benzylpenicillin or feneticillin. Co-amoxiclav and clindamycin are alternative options. Clindamycin is recommended in case of beta-lactam allergies, and inhibits streptococcal and staphylococcal toxin production. Clindamycin is also thought to have better tissue penetration than beta-lactams. However, clindamycin is highly concentrated intracellularly, and studies measuring tissue concentrations used homogenised tissues and thus also measured intracellular clindamycin.[88] This overestimates relevant clindamycin levels in the extracellular fluid, while the primarily extracellular beta-lactam concentration is diluted by the released intracellular volume and thus underestimated.[88] Of note, some *S. aureus* strains have inducible resistance for clindamycin, showing growth inhibition in vitro but resistance in vivo.[89,90] In the Netherlands, around 10% of *S. aureus* from selected general practice patients and hospital patients show (inducible) resistance to clindamycin, compared with less than 3% for flucloxacillin.[90] This makes clindamycin less preferable as an empirical choice.

Evidence does not favour one agent over others, although there is a major lack of evidence in this area.[91] One study found pristinamycin to be slightly more efficacious than penicillin in a non-blinded trial, but did not account for penicillin not covering *S. aureus*.[3,92] Beta-lactams were as effective as non-beta-lactams in a cohort study.[93] A recent meta-analysis comparing penicillins or cephalosporins with macrolides or lincosamides (such as clindamycin) found similar efficacy between the two groups.[94]

If one needs to cover multi-resistant *Staphylococcus aureus* (MRSA), vancomycin remains the first choice of treatment, with linezolid as an alternative.[95] Additionally, three novel antibiotics have recently been approved by the European Medicines Agency for treatment of skin infections: oritavancin and dalbavancin, two (lipo)glycopeptides, and

Table 3. *Conditions with possible atypical pathogens*

Condition	Possible atypical pathogens
Neutropenia[80]	*Escherichia coli* Enterobacteriaceae *Pseudomonas aeruginosa*
Liver cirrhosis[81,82]	*E. coli*, *Klebsiella* spp, *Pseudomonas* spp, *Proteus* spp, *Aeromonas* spp, *Vibrio* spp, *Acinetobacter* spp
Diabetic foot infection[83]	
- Chronic ulcer, or ulcer previously treated with antibiotics	Enterobacteriaceae
- Macerated ulcer	*P. aeruginosa* (in combination with other organisms)
- Long duration nonhealing wounds with prolonged, broad-spectrum antibiotic treatment	Enterococci, diphtheroids, Enterobacteriaciae, *Pseudomonas* spp, nonfermentative gram-negative rods
Fresh or salt water exposure[84]	*Aeromonas hydrophila*, *Edwardsiella tarda*, *Erysipelothrix rhusiopathiae*, *Mycobacterium fortuitum*, *Mycobacterium marinum*, *Shewanella putrefaciens*, *Streptococcus iniae*
- Tropical/warm water	*Chromobacterium violaceum*, *Vibrio vulnificus*
Fish fin or bone injuries[84,85]	*Enterobacter* spp, *Erysipelothrix rhusiopathiae*, *Klebsiella pneumoniae*, *Mycobacteria marinum*, *Streptococcus iniae*, *Vibrio vulnificus*
Human bites[86]	*Eikenella corrodens*, *Haemophilus* spp, Enterobacteriaceae, *Gemella morbillorum*, *Neisseria* spp, *Prevotella* spp, *Fusobacterium* spp, *Eubacterium* spp, *Veillonella* spp, *Peptostreptococcus* spp
Cat or dog bites[86]	*Pasteurella* spp, *Neisseria* spp, *Corynebacterium* spp, *Moraxella* spp, *Enterococcus* spp, *Fusobacterium* spp, *Porphyromonas* spp, *Prevotella* spp, *Propionibacterium* spp, *Bacteriodes* spp, *Peptostreptococcus* spp

tedizolid, an oxazolidinone, all showing potent activity against MRSA similar to vancomycin and linezolid (*table 4*).[96] Oritavancin and dalbavancin both have terminal half-lives of over two weeks and thus only require a single intravenous dose to reach cure rates non-inferior to a 2-week course of vancomycin.[98,103] Whether this actually reduces the number of admissions or total treatment costs remains to be evaluated.

Optimising antibiotic use

For oral flucloxacillin, proper timing of intake (before or long after meals) optimises the bioavailability to ~55%.[104] Beta-lactams reach lower serum concentrations in obese patients due to altered distribution volumes and clearance, so these patients might benefit from higher oral dosing, or more frequent intravenous dosing.[105] This is underscored by the fact that obese patients tend to have lower cure rates.[106,107]

The optimal duration of antibiotic treatment of cellulitis is unknown. One study suggested that patients with cellulitis who are treated on an outpatient basis only require 5 days of therapy when signs of improvement are seen.[108] However, this study used unconventional numbers for its power calculation, had a dropout rate of 30% before randomisation due to non-improvement, included relatively young and healthy subjects and made use of levofloxacin as study drug.[11] Community-acquired pneumonia, pyelonephritis and intraabdominal infections require shorter antibiotic treatments than we previously thought necessary.[109-111] Whether cellulitis treatment can also be shortened is under investigation.[112]

Some patients have an increased risk of a complicated infection. Obesity predisposes to local complications such as bullae, abscess formation, haemorrhagic lesions and necrosis.[113,114] Smoking and delays in antibiotic treatment are also linked to abscess formation.[113] Patients with congestive heart failure, neutropenia, hypoalbuminaemia, an altered mental status or discharge from the lesion have an increased risk of experiencing adverse outcomes, in terms of death, local complications (e.g. requiring surgical drainage) or systemic complications (e.g. multi-organ failure).[7]

Non-antibiotic management

Additional non-antibiotic management options can potentially improve outcomes. Compression therapy has

Table 4. *New antibiotics for skin and soft tissue infections*

Agent	Dosing	Dose adjustments for kidney function	Early clinical response (mITT)*	Investigator assessed clinical cure post-treatment (mITT)*	Cellulitis specific*	Inclusion criteria for study population	Notes
Dalbavancin[96,97]	1500 mg iv once, or two once-weekly doses of 1000 mg iv and 500 mg iv	75% of dose in creatinine clearance <30 ml/min	80% vs 80%	96% vs 97%	79% vs 77% ECR; 91% vs 92% CSEOT	- 85 ≥ age ≥ 18 - Wound infection, cellulitis or major cutaneous abscess, each with a minimum surface area of 75 cm^2 (or 50 cm^2 for face cellulitis) - Suspected or confirmed gram-positive bacteria - Hospitalised for at least 3 days of intravenous antibiotics - At least two local and one systemic signs of infection	Comparator is vancomycin CSEOT = decrease in lesion size from baseline, temp ≤ 37.6, no fluctuance or heat/warmth, tenderness/induration no worse than mild, at end of therapy. Increased ALT/AST levels, 12% of patients have reduced platelets
Oritavancin[96,98,99]	1200 mg iv once	None	80-82% vs 79-83%	80%-83% vs 80-81%	67% vs 75% ECR; 71% vs 76% PTE	- Age ≥ 18 - Wound infection, cellulitis/erysipelas (onset within 7 days prior) or major cutaneous abscess, each with a minimum surface area of 75 cm^2 - Suspected or confirmed gram-positive bacteria - Hospitalised for at least 7 days of intravenous antibiotics - At least two local and one systemic signs of infection	Comparator is vancomycin Serious hypersensitivity reactions reported. Caution warranted in case of allergy to other glycopeptides, including vancomycin. Falsely elevated PT and PTT, increases bleeding risk of warfarin. Relatively healthy study population in registration trials

Agent	Dosing	Dose adjustments for kidney function	Early clinical response (mITT)*	Investigator assessed clinical cure post-treatment (mITT)*	Cellulitis specific*	Inclusion criteria for study population	Notes
Tedizolid[100-102]	Once daily 200 mg iv or po, 6 days	None	82% vs 79%	87% vs 87%	78% vs 76% ECR; 88% vs 82% IACPT	- Age ≥ 12 - Wound infection, cellulitis/ erysipelas or major cutaneous abscess, each with a minimum surface area of 75 cm² and onset within 7 days prior - Suspected or confirmed gram-positive bacteria - Minimum of local and systemic signs of infection depend on infection type	Comparator is linezolid Cellulitis-specific investigator-assessed post-treatment cure rate only available from ESTABLISH-I

mITT = modified intention to treat; IV = intravenous; *all percentages are listed as success chance in investigational treatment group vs comparator group, no differences were statistically significant; ECR = early clinical response; CSEOT = clinical status at end of therapy; WBC = white blood cell; IACPT = investigator-assessed cure post treatment; PTE = post-treatment evaluation.

long been, and still is, cause for debate. Advocates claim there is an accelerated reduction of oedema and pain, and shorter time to cure. Currently, no evidence supports this claim. Patients, however, often report side effects such as pain, dry skin, itching, constriction and slipping.[115,116] It is unknown if the altered haemodynamics affect the time to microbiological cure. The adequacy of applied bandages varies in clinical practice, and inadequately applied bandages can cause pressure ulceration, thus unnecessary harm.[117,118] An alternative to reduce oedema in the acute phase is passive leg elevation. To prevent persisting lymphoedema from causing recurrences, compression therapy is indicated when lymphoedema persists for several weeks after antibiotic treatment.[11] Compression stockings should follow initial bandaging, provided the patient's arterial disease status allows it.[118]

The use of anti-inflammatory drugs in addition to antibiotic therapy might be beneficial. In a proof-of-concept study, adjunctive non-steroidal anti-inflammatory drugs (NSAIDs) led to faster regression and resolution of symptoms.[119] Similarly, patients receiving adjunctive oral prednisone (2 days 30 mg, 2 days 15 mg, 2 days 10 mg, 2 days 5 mg) had earlier resolution of symptoms and intravenous to oral antibiotic switches.[120,121] Whether these drugs also affect microbial eradication is as yet unknown.

Recurrent cellulitis

Almost 30% of admissions for cellulitis are for recurrent cellulitis.[122] Two, three and five year recurrence rates are 17%, 29-47% and 47%, respectively.[38,123-125] Five-year recurrence rate is 57% in patients with a history of recurrence.[125] For HIV-infected patients, one- and three-year recurrence rates are 29% and 47%.[126] Independent of persisting risk factors that might explain recurrences, the first episode's inflammation has also likely damaged local lymphatic channels. Drainage is then insufficient, antigen presenting cells cannot migrate, and accumulating protein-rich fluid accommodates invading bacteria.[127]

Lymphoedema is the most important risk factor for recurring cellulitis, and 25-60% of recurrent cellulitis patients suffer from chronic oedema.[122,124] Obese patients have more recurrences and CRP and leucocyte counts are higher in these recurrences.[39] For HIV-infected patients specifically, non-hepatitis liver disease, intravenous catheters or intravenous drug use increase the recurrence

Textbox 3. Questions for future research

What is the best way to...
... distinguish cellulitis from its mimickers?
... obtain a representative microbiological diagnosis?
... effectively reduce recurrences?

What is the role of...
... the skin microbiota in the aetiology of cellulitis?
... compression therapy in its management?
... anti-inflammatory agents in disease management?
... pathogen reservoirs in recurrences?

Which patients are likely to...
... not require antibiotics at all?
... succeed with a shortened treatment duration?
... fail on outpatient therapy?
... require higher doses of antibiotics?
... require extended treatments?

risk.[126] All persisting risk factors are also likely to increase the chance of recurrences, and should be treated vigorously when possible. Lymphoedema warrants treatment with compression therapy. Tinea pedis should be treated with topical azoles in order to decrease the chance of recurrence. Frequent and meticulous interdigital web space cleansing prevents skin damage, bacterial overgrowth and bacterial invasion.[127]

S. pyogenes is able to survive and replicate within macrophages.[128] Theoretically this might elicit recurrences. However, recurrence rates are similar between patients receiving antibiotics with or without intracellular activity.[129] When infections recur despite adequately treating risk factors, prophylactic antibiotics prevent recurrences.[130] In the PATCH I trial, which randomised 274 patients with two or more episodes to either twice daily low-dose oral penicillin or placebo, recurrence rates were significantly lower in the penicillin group (22% vs 37%) after one year, although this effect wore off after cessation of treatment.[131] For recurring *S. aureus* infections, on-demand therapy can be considered. *S. aureus* eradication or hygiene measures do not prevent recurrent *S. aureus* skin infections.[132,133]

Future perspectives

An overview of knowledge gaps which, if addressed, could advance our understanding of the pathophysiology of cellulitis and improve its clinical management is given in *textbox 3*. A major challenge is the high rate of misdiagnoses which can bias clinical trials towards non-inferiority.[70] To determine applicability and reliability of trial results, it is imperative to document results from abscesses and cellulites separately, to accurately describe criteria and definitions, to extensively document clinical and microbiological characteristics, and to report information on additional procedures such as surgical drainage or limb immobilisation.[134] For this relatively simple infection which has plagued humanity for so long, there still is a lot to discover.

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ORIGINAL ARTICLE

Optimising the ISAR-HP to screen efficiently for functional decline in older patients

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ABSTRACT

Introduction: The Identification of Seniors At Risk-Hospitalised Patients (ISAR-HP) has recently been included in guidelines as a frailty indicator to identify patients for comprehensive geriatric assessment. Previous studies showed that the conventional cut-off score incorrectly classifies a high percentage of patients as high risk. We aimed to optimise the predictive value of ISAR-HP by using different cut-offs in older acutely hospitalised patients.
Methods: A prospective follow-up study was performed in two Dutch hospitals. Acutely hospitalised patients aged ≥ 70 years were included. Demographics, illness severity parameters, geriatric measurements and the ISAR-HP scores were obtained at baseline. The primary outcome was a combined end point of functional decline or mortality during 90-day follow-up.
Results: In total 765 acutely hospitalised older patients were included, with a median age of 79 years, of whom 276 (36.1%) experienced functional decline or mortality. The conventional ISAR-HP cut-off of ≥ 2 assigned 432/765 patients (56.5%) as high risk, with a positive predictive value (PPV) of 0.49 (95%CI 0.45-0.54) and a negative predictive value of 0.81 (95%CI 0.76-0.85). Thus, 51% of those whom the ISAR-HP denoted as high risk did not experience the outcome of interest. Raising the cut-off to ≥ 4 assigned 205/765 patients (26.8%) as high risk, with a marginally increased PPV to 0.55 (95%CI 0.48-0.62).
Conclusion: The ISAR-HP with the conventional cut-off of ≥ 2 incorrectly identifies a large group of patients at high risk for functional decline or mortality and raising the cut-off to 4 only marginally improved performance. Caution is warranted to ensure efficient screening and follow-up interventions.

KEYWORDS

ISAR-HP, cut-off points, older patients, hospitalisation, functional decline

INTRODUCTION

In the Netherlands, at the suggestion of both the Health Care Inspectorate (IGZ) and insurance companies, the Identification of Seniors At Risk – Hospitalised Patients (ISAR-HP) screening instrument is currently being promoted for use as a frailty indicator, for example in older patients with an indication for colon surgery.[1] Comprehensive geriatric assessment (CGA) is subsequently advised for 'frail' patients in order to prevent functional decline. Identification of patients at high risk for functional decline is essential to ensure that interventions are targeted effective at those who will benefit most.[2]
The ISAR-HP is a recently developed screening instrument to predict 90-day functional decline in older patients who were acutely admitted to the department of internal medicine.[3] Test characteristics were reasonable with respect to discrimination (area under the receiver operating curve, AUC), but the positive predictive value was rather low. Using the conventional cut-off score of ≥ 2 classified more than half of all older patients as being at risk for functional decline.[3,4] However, classification was incorrect for 57% of the internal medicine patients in the development cohort and 64% of older patients undergoing cardiac surgery in a validation cohort, because no functional decline was experienced.[3,4] As a consequence it is questionable whether using intensive interventions,

such as the relatively time-consuming CGA, can be cost-effective.

The aim of the present study was to evaluate the performance of the ISAR-HP in predicting adverse health outcomes in acutely hospitalised older patients in two hospitals in the Netherlands. Predictive performance was tested by using different cut-off points of the ISAR-HP for predicting functional decline or mortality.

METHODS

Study design and setting

The Acutely Presenting Older Patients (APOP) study is a prospective multicentre cohort study in older patients visiting the emergency department. Data were collected in the emergency departments of the Leiden University Medical Center from September 2014 until November 2014 and the Alrijne Hospital Leiderdorp from March 2015 until May 2015. In both hospitals patients were included 7 days a week for a period of 12 weeks. The inclusion criterion of the APOP study was all patients aged 70 years and older who visited the emergency department. Exclusion criteria were red on the Manchester Triage System (i.e. patients requiring acute medical attention, such as cardiopulmonary resuscitation), an unstable medical condition, refusal to participate by the patient, an impaired mental condition of patients in the absence of a proxy to provide informed consent, and presence of a language barrier. For the current analyses, all acutely hospitalised patients of the APOP cohort with an ISAR-HP score at baseline were included. The ISAR-HP scores were calculated afterwards and not noted in the patient records, to ensure that all patients received usual care. Written informed consent was obtained from all patients. The Medical Ethics Committee of the Leiden University Medical Center and Alrijne Hospital approved the study. A more detailed description of the study design can be found in a previously published paper.[5]

Characteristics

Baseline characteristics included age, gender, living situation, level of education, clinical specialism, number of medications, history of dementia, Katz ADL score and cognitive impairment. Independent living situation represents patients living independently on their own or with others, high education was defined as higher vocational training or university, and number of medications represents the number of medications used at home as reported by the patient. Clinical specialism corresponds to the responsible specialism on the ward patients were admitted to. The cognitive status was assessed with the six-item Cognitive Impairment Test (6CIT);[6] this score ranges from 0 to 28, with a score of 11 or higher indicating moderate to severe cognitive impairment.[7] Functionality two weeks prior to admission was evaluated by means of the Katz ADL score, which contains six items: bathing, dressing, toileting, transferring, eating and the use of incontinence material.[8] Each item is scored as independent (0 points) or dependent (1 point), with higher scores corresponding to more dependency.

ISAR-HP

The ISAR-HP is a scorecard with four yes/no questions on needing assistance on a regular basis, use of a walking device, needing assistance for travelling and having received education after the age of 14 years *(Appendix, figure 1)*.[3] The score ranges from 0 to 5 with a score of 2 or more indicating a high risk of functional decline. The originally developed regression model of the ISAR-HP was: 1 / 1 + exp (– (–1.93 + 0.48 × 'pre-admission need for assistance in IADL on a regular base' + 0.81 x 'use of a walking device' + 0.57 x 'need of assistance in travelling' + 0.42 × 'no education after age 14')).

Outcomes

Originally the ISAR-HP was developed for predicting solely functional decline,[3] but at the moment of obtaining an ISAR-HP score it is impossible to distinguish patients who will not die within 90 days of follow-up from those who will. Therefore, in the present study the ISAR-HP was validated for predicting the composite outcome of functional decline or mortality within 90 days of follow-up after hospital admission. Information on functional dependency was assessed by telephone. Functional decline was defined as either an increase of at least 1 point on the Katz ADL score 90 days after hospitalisation compared with two weeks prior to admission or moving from an independent living situation to a dependent living situation. Dates of death were obtained from the Dutch municipality records.

Additionally, the ISAR-HP was validated for solely functional decline, for which we used the same exclusion criteria as the development study.[3] Patients with a maximum Katz ADL score at baseline (fully dependent patients) and patients living in a nursing home at baseline were excluded, because these patients could not decline further as defined in our study. Also patients who were lost to follow-up or died within 90 days were excluded.

Statistical analysis

The baseline characteristics are presented as numbers with percentages or medians with interquartile ranges (IQR). A minimum of 100 events was considered necessary to provide sufficient statistical power for external validation.[9] Predictive performance of the ISAR-HP was assessed by examining measures of discrimination and calibration.

Discrimination of the ISAR-HP score was quantified by calculating the AUC. The sensitivity, specificity, positive and negative predictive values (PPV and NPV) and positive and negative likelihood ratio were calculated for using the conventional cut-off of ≥ 2 points, but also using other thresholds of the ISAR-HP score (≥ 1, ≥ 3 and ≥ 4). Calibration of the internally validated ISAR-HP regression equation was assessed by plotting observed versus predicted probabilities, calculating calibration slope and with a goodness-of-fit test (Hosmer and Lemeshow test[10]). Data were analysed using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY) and R Statistics version 3.3.0.[11].

RESULTS

In the APOP study, 1965 consecutive older patients visiting the emergency department of the Leiden University Medical Center or Alrijne Hospital were eligible for participation. In total 1632 patients (83.1%) were included after informed consent, of whom 771 (42.2%) were subsequently hospitalised. After exclusion of three missing and three incomplete ISAR-HP scores, the study population for the present analyses contains 765 patients. *Table 1* shows the baseline characteristics of the study population. The median age was 79 years (IQR 74-84), 374 patients (48.9%) were male and 698 patients (91.2%) were living independently either on their own or with others. Most patients were admitted for the clinical specialism internal medicine (242 patients, 36.1%), cardiology (168 patients, 22.0%) or surgery/orthopaedics (154 patients, 20.1%). The median Katz ADL score was 0 (IQR 0-2) and 172 patients (25.1%) had cognitive impairment.

Figure 1 displays the distribution of ISAR-HP scores. The median ISAR-HP score was 2 (IQR 0-4) and 432 patients (56.5%) were at high risk for functional decline or mortality when using the conventional cut-off of ≥ 2.

In total 276 patients (36.1%) experienced functional decline or mortality within 90 days of follow-up. We first performed an external validation of the ISAR-HP. *Figure 2* shows the calibration plot of the ISAR-HP for functional decline or mortality. Calibration was insufficient with a Hosmer and Lemeshow goodness-of-fit p-value of 0.007. Predicted probabilities were lower than the observed probabilities with a calibration slope of 0.877 and an intercept of 0.246, indicating an underestimation of the outcome.

The predictive performance of the ISAR-HP is shown in *table 2*. Accuracy of the ISAR-HP was reasonable, with an AUC of 0.69 (95%CI 0.65-0.73). External validation of the ISAR-HP for the conventional cut-off of ≥ 2 resulted in a sensitivity of 0.77 (95% CI 0.72-0.82), a specificity of 0.55 (95 %CI 0.51-0.60), a PPV of 0.49 (95% CI 0.45-0.54) and an NPV of 0.81 (95% CI 0.76-0.85). Using the cut-off of ≥ 2, 51% of the patients were incorrectly considered to be at high risk and 19% were incorrectly considered low risk. Predictive performance of different cut-off points was calculated to assess the change in PPV and NPV for

Table 1. *Baseline characteristics of acutely hospitalised older patients*

	n = 765
Age, median (IQR)	79 (74-84)
Male, n (%)	374 (48.9%)
Independent living arrangements, n (%)	698 (91.2%)
High education, n (%)	143 (18.7%)
Academic hospital, n(%)	331 (40.7%)
Clinical specialism, n (%)	
- Internal medicine	242 (36.1%)
- Cardiology	168 (22.0%)
- Surgery/Orthopaedics	154 (20.1%)
- Neurology	87 (11.4%)
- Pulmonology	73 (9.5%)
- Others[1]	41 (5.4%)
Number of medications, median (IQR)	6 (3-8)
History of dementia, n (%)	33 (4.3%)
Katz ADL score, median (IQR)[2]	0 (0-2)
Cognitive impairment, n (%)[3]	172 (25.1%)

IQR = interquartile range; ADL = activities of daily living. [1]Others includes gastroenterology, urology, ear nose throat and oncology, all contributing < 3.0%. [2]The Katz ADL score indicates functional status two weeks prior to admission with scores ranging from 0-6. A higher score corresponds with more dependency. In total 15 Katz ADL scores were missing. [3]Cognitive impairment indicates patients with a 6CIT (six-item cognitive impairment test) score of ≥ 11. In total 81 6CIT scores were missing.

Figure 1. *Histogram of ISAR-HP scores*

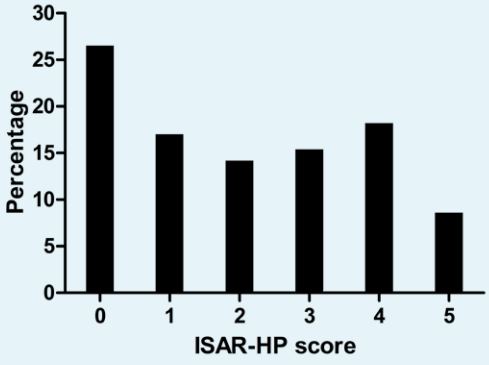
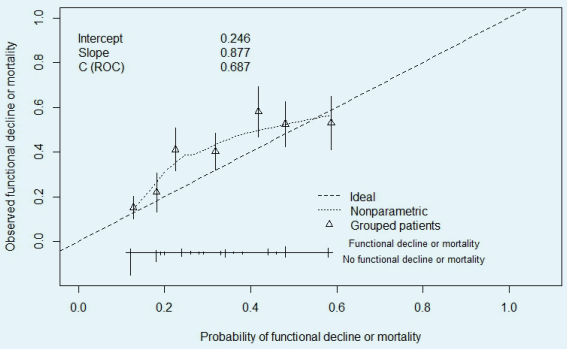


Figure 2. *Calibration plot of the predicted probabilities for 90-day functional decline or mortality with the original internal validated ISAR-HP regression equation. The vertical lines represent the relative frequency distribution of predicted probabilities of patients experiencing the combined outcome (above the horizontal line) or not experiencing the outcome (below horizontal line). The triangles represent the grouped patients with 95% confidence intervals. The Hosmer and Lemeshow goodness-of-fit p-value is 0.007*



experiencing functional decline or mortality. An ISAR-HP cut-off of ≥ 1 assigned 562/765 patients (73.5%) to high risk, with a PPV of 0.44 (95%CI 0.39-0.48), an NPV of 0.85 (95%CI 0.79-89), resulting in incorrect classification of 56% of the high-risk and 15% of the low-risk patients. By using the strict cut-off of ≥ 4 in total 205/765 patients (26.8%) were assigned to high risk, with a PPV of 0.55 (95%CI 0.48-0.62), an NPV of 0.71 (95%CI 0.67-0.74), which results in 45% incorrectly classified high-risk patients and 29% incorrectly classified low-risk patients. Additionally, although of limited clinical applicability, we validated the ISAR-HP for solely functional decline to allow comparison of performance compared with the original study (*Appendix: table 1* and *figure 2*). After applying the exclusion criteria for functional decline (113 patients died, 30 patients were lost to follow-up, 17 patients were unable to demonstrate functional decline and 13 patients refused), 592 patients were included of whom 162 (27.4%) experienced functional decline. Discrimination was fair (AUC 0.72, 95% CI 0.67-0.76) and calibration satisfactory (Hosmer and Lemeshow goodness-of-fit p-value 0.068). The PPV and NPV were lower for all cut-offs, with a PPV of 0.42 (95%CI 0.37-0.48) and NPV of 0.89 (95%CI 0.84-0.92) for an ISAR-HP score of ≥ 2.

DISCUSSION

The main finding of the present study is that the ISAR-HP with the conventional cut-off of ≥ 2 resulted in more than half of all acutely admitted patients to be considered at high risk for 90-day functional decline or mortality; of these patients 51% did not experience this outcome. Raising the ISAR-HP cut-off to ≥ 4 resulted in a quarter of all patients being classified at high risk and the predictive performance increased marginally.

The ISAR-HP was originally developed to predict 90-day functional decline in patients aged 65 years and older, who were acutely hospitalised for at least 48 hours on a general internal medicine ward.[3] Age and gender were comparable, but compared with our cohort more patients were living dependently (24% in development cohort vs. 9% in APOP cohort) and more patients were cognitively impaired (34% in development cohort vs. 25% in APOP

Table 2. *Predictive performance of the ISAR-HP with different cut-off points for the composite outcome 90 days after acute hospitalisation in older patients*

	High risk n, (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% C)	LR- (95% CI)
ISAR-HP ≥ 1	562 (73.5%)	0.89 (0.84-0.92)	0.35 (0.31-0.40)	0.44 (0.39-0.48)	0.85 (0.79-0.89)	1.37 (1.27-1.48)	0.32 (0.23-0.45)
ISAR-HP ≥ 2	432 (56.5%)	0.77 (0.72-0.82)	0.55 (0.51-0.60)	0.49 (0.45-0.54)	0.81 (0.76-0.85)	1.72 (1.53-1.94)	0.41 (0.33-0.52)
ISAR-HP ≥ 3	323 (42.2%)	0.59 (0.53-0.65)	0.67 (0.63-0.71)	0.50 (0.45-0.56)	0.74 (0.70-0.78)	1.80 (1.53-2.12)	0.61 (0.53-0.70)
ISAR-HP ≥ 4	205 (26.8%)	0.41 (0.35-0.47)	0.81 (0.77-0.84)	0.55 (0.48-0.62)	0.71 (0.67-0.74)	2.13 (1.69-2.69)	0.73 (0.66-0.81)

CI = confidence interval; PPV = positive predictive value; NPV=negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio. The area under receiver operating curve of the ISAR-HP model was 0.69 (95% CI 0.65-0.73).

cohort). In the original development study 70% of all older patients were identified as high risk with a PPV of 0.43, implying that 57% of these high-risk patients did not suffer from functional decline. In the APOP cohort 57% were assigned as high risk with a PPV of 0.49, which means 51% showed no decline. The ISAR-HP was also validated for functional decline in cardiac surgery patients aged 65 years and older.[4] Compared with the APOP cohort the patients were younger (mean age 73 years), more often male (64%) and had a better cognitive performance (14% with memory problems). In total 16% of the cardiac surgery patients suffered a functional decline and the AUC of the ISAR-HP was 0.72. The reported PPV of an ISAR-HP score of ≥ 2 was 0.36, which implies that approximately two out of three patients were incorrectly considered high risk. Results from a meta-analysis of screening instruments to predict functional decline and mortality in older patients visiting the emergency department were in line with the results of the ISAR-HP.[12] High-risk groups could not accurately be distinguished from low-risk groups and a relatively high number of patients were incorrectly classified as high risk. In the Netherlands older hospitalised patients are systematically screened for undernutrition, ADL limitations, falls and delirium to prevent 90-day functional decline or mortality: the Safety Management System (VMS+) screening.[13] A third of all VMS+ screened older patients were considered to be at high risk and predictive performance was comparable with our results, with a PPV ranging between 0.50 and 0.57. In summary, the results of our study were in line with ISAR-HP in older patients on both a general internal medicine ward and undergoing cardiac surgery and in line with the performance of the VMS+ screening.

The ISAR-HP was developed and validated to predict only functional decline. In order to replicate that analysis, we had to exclude almost a quarter of patients due to the exclusion criteria, including those who had died during follow-up. As a consequence, this selection no longer reflects clinical practice, where screening is implemented for all patients. A composite outcome of functional decline with mortality as ultimate decline in physical functioning was therefore used. In the present study the predictive performance of different cut-off points for predicting the composite outcome was studied in order to improve efficiency of ISAR-HP screening. Increasing the cut-off point to ≥ 4 resulted in selection of 26.8% of the patients at highest risk and the PPV improved to 55%. Although one in two patients would be inappropriately assigned to the 'high-risk' group, less patients are considered at high risk. To date, the ISAR-HP has been used twice in study settings as a screening instrument for CGA interventions to specifically prevent functional decline in older hospitalised patients. In the Prevention and Reactivation Care Program (PReCaP) older patients at risk of functional decline received supplementary multidisciplinary, goal-oriented care.[14] In the Transitional Care Bridge Randomised Controlled Trial older patients at risk of functional decline received a systematic CGA, followed by a hospital visit of the community care registered nurse and subsequent multiple home visits after discharge.[15] Although the interventions should be appropriate to prevent functional decline, both the PReCap and the Transitional Care Bridge Randomised Controlled Trial showed no effect on ADL functioning. Based on the findings of our study this may be explained by the fact that many patients were incorrectly selected for the intervention. Taken together, the predictive performance of the ISAR-HP is characterised by low PPVs. Using the ISAR-HP for identifying patients at high risk for functional decline could result in providing inefficient follow-up care.

In screening instruments there is a certain clinical threshold which is determined by the relative weight of false-negative versus false-positive errors. A conservative low cut-off is useful if missing a patient who will undergo a functional decline is more important than incorrect classification of a patient who will not.[16] From the patient perspective a low cut-off is desirable, especially if it results in an intervention without side effects. However, using a stricter cut-off is more useful from another perspective. As an example, in 2012 in total 734,000 patients aged 65 years and over were admitted to hospital in the Netherlands (25% of all older adults)[17] of whom 415,000 might have been at high risk according to our results with the conventional ISAR-HP cut-off of ≥ 2. If the recommended CGA had been performed in all patients, 212,000 CGAs would be carried out unnecessarily in order to prevent the occurrence of the outcome. Using a stricter ISAR-HP cut-off ≥ 4 would result in 197,000 high-risk patients, with 88,000 incorrectly classified as high risk. In patient groups with a lower incidence of functional decline or mortality, such as older cardiac surgery patients, even more interventions will be performed unnecessarily.[4]

Taking into account the limited efficacy and capacity to perform CGAs we therefore recommend to target interventions in a larger group of patients which are inexpensive, less time consuming and not a burden for the patient. A more specific screening instrument for hospitalised older patients is needed to be able to target resource intensive interventions in a smaller group of patients. In our publication on the development and validation of a new screening instrument for older patients visiting the emergency department, we were able to increase specificity compared with the widely accepted ISAR screening instrument.[5] During hospital stay more patient data will become available, such as vital parameters and laboratory results, which may improve predictive performance. Therefore, we are currently developing a new dynamic predicting model for hospitalised older patients.

Several limitations need to be addressed. First, the performance of the ISAR-HP in non-acutely hospitalised older patients, such as elective admissions and via the outpatient clinic, has not been evaluated. Second, the follow-up data on functional decline were incomplete for 43 patients. From municipal records we know that these patients were alive, which might therefore have resulted in an underestimation of functional decline. The major strength of the study is the inclusion of a representative cohort of older patients. In total 83% of the eligible older patients from different specialisms were included, from both an academic and regional hospital. A second strength is that ISAR-HP was evaluated for the composite outcomes, which reflects predictive performance in clinical practice.

In conclusion, the ISAR-HP with the conventional cut-off of ≥2 incorrectly identifies a large group of patients as being at high risk for functional decline or mortality, and raising the cut-off to 4 only marginally improved performance. Caution is warranted to ensure efficient screening and follow-up interventions.

DISCLOSURES

The authors declare no conflict of interest.
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APPENDIX

Figure 1. *Scorecard of the Identification of Seniors at Risk – Hospitalised Patients*

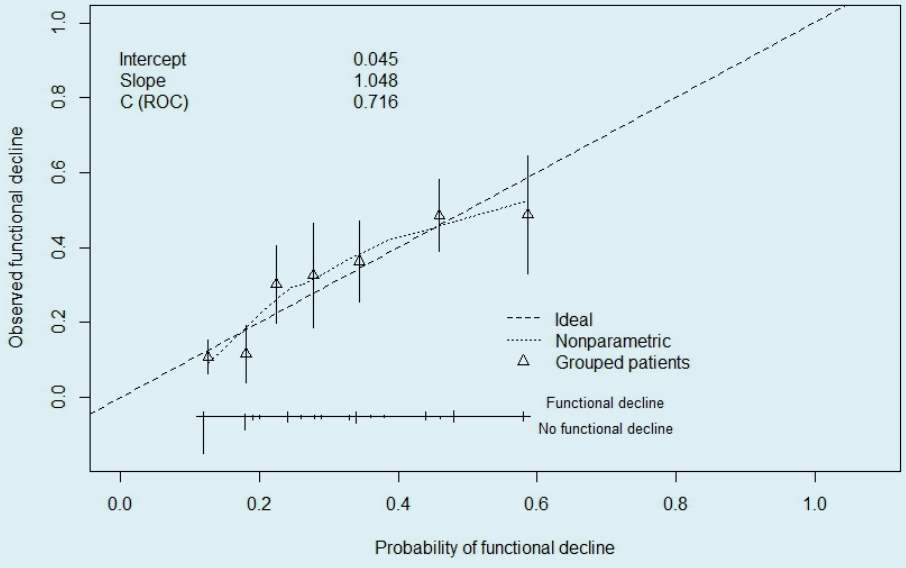
ISAR-HP		
	YES	**NO**
Before hospital admission, did you need assistance for IADL on a regular basis? (e.g. assistance in housekeeping, preparing meals, shopping, etc.)	1	0
Do you use a walking device? (e.g. a cane, rollator, walking frame, crutches, etc.)	2	0
Do you need assistance for travelling?	1	0
Did you continue education after age 14?	0	1
Total score (circled figures)		
Total score 0 or 1 = not at risk **Total score ≥ 2 = patient is at risk for functional decline**		

Table 1. *Predictive performance of the ISAR-HP with different cut-off points for functional decline within 90 days after acute hospitalisation in older patients*

	High risk n, (%)	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**
ISAR-HP ≥ 1	407 (68.8%)	0.88 (0.81-0.92)	0.38 (0.34-0.43)	0.35 (0.30-0.40)	0.89 (0.84-0.93)	1.42 (1.29-1.56)	0.32 (0.21-0.49)
ISAR-HP ≥ 2	305 (51.5%)	0.80 (0.72-0.85)	0.59 (0.54-0.64)	0.42 (0.37-0.48)	0.89 (0.84-0.92)	1.95 (1.70-2.23)	0.34 (0.25-0.47)
ISAR-HP ≥ 3	219 (37.0%)	0.60 (0.52-0.67)	0.72 (0.67-0.76)	0.44 (0.38-0.51)	0.83 (0.78-0.86)	2.11 (1.73-2.57)	0.56 (0.46-0.68)
ISAR-HP ≥ 4	132 (22.3%)	0.41 (0.33-0.49)	0.85 (0.81-0.88)	0.50 (0.41-0.59)	0.79 (0.75-0.83)	2.65 (1.99-3.55)	0.70 (0.62-0.80)

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.
The area under receiver operating curve of the ISAR-HP model was 0.72 (95% CI 0.67-0.76). In total 162/592 patients (27.4%) experienced functional decline.

Figure 2. *Calibration plot of the predicted probabilities for 90-day functional decline with the original internal validated ISAR-HP regression equation. The vertical lines represent the relative frequency distribution of predicted probabilities of patients experiencing functional decline (above the horizontal line) or not experiencing functional decline (below horizontal line). The triangles represent the grouped patients with 95% confidence intervals. The Hosmer and Lemeshow goodness-of-fit p-value is 0.068*



ORIGINAL ARTICLE

Non-targeted HIV screening in emergency departments in the Netherlands

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ABSTRACT

Background: In the Netherlands a substantial proportion of newly diagnosed human immunodeficiency virus (HIV) patients present late for care and an estimated 12-34% of people living with HIV are undiagnosed. Linkage to care of these patients is important to decrease HIV transmission and to improve individual patient outcomes. We investigated if non-targeted HIV testing in emergency departments is a useful and cost-effective way to identify these patients.

Methods: In a cross-sectional multicentre study, eligible adult patients who underwent phlebotomy were given an active choice to be additionally tested for HIV. In a subset of patients, risk factors for HIV infection were asked for. A cost-effectiveness analysis was conducted.

Results: Of 7577 eligible patients, 3223 patients were tested, and two new HIV infections were diagnosed (0.06%). Both patients had risk factors for HIV infection. Non-targeted HIV testing in the emergency department was not considered cost-effective, with a cost per quality adjusted life years gained of € 77,050, more than triple the Dutch cost-effectiveness threshold of € 20,000.

Conclusion: Non-targeted HIV testing in emergency departments in the Netherlands had a low yield of newly diagnosed HIV infections and was not cost-effective. Our data suggest that targeted HIV testing may offer an alternative approach to decrease the number of undiagnosed people living with HIV.

KEYWORDS

Cost effectiveness, emergency department, HIV, screening

INTRODUCTION

Early identification of patients infected with the human immunodeficiency virus (HIV) has been associated with benefits for both the individual and public health.[1-3] From a public health perspective, early identification provides the opportunity to change risk behaviour and allows for earlier initiation of combination antiretroviral therapy (cART). This so-called 'treatment as prevention' has been shown to prevent onward HIV transmission.[1,4] Clinically, late presentation of HIV-infected patients (CD4 cell count 350 cells/µl) increases the risk of death in the first year after diagnosis tenfold and leads to a decrease in life expectancy of ten years.[5] Early initiation of cART has been shown to decrease morbidity and mortality, resulting in a life expectancy equal to that of the general population.[2,6]

Recent data show that in the USA an estimated 13% of persons living with HIV are still undiagnosed.[7] Worldwide 17.1 million people living with HIV do not know they are infected with the virus.[8] In the Netherlands, by the end of 2014, 12-34% of HIV-infected individuals (depending on the method used[9,10]) are estimated to be unaware of their infection. This is higher than the goal set by the Joint United Nations Program on HIV/AIDS (UNAIDS) that 90% of all people living with HIV should be aware of their HIV status.[11] Diagnosis of HIV infections and subsequent linkage to care should therefore be scaled up. From 2006 the Center for Disease Control and Prevention (CDC) has recommended routine HIV screening at emergency departments (EDs) in the USA.[12] Using different screening methods in different countries (UK, USA and Spain), prevalence of HIV infection among ED patients varied from 0.28% to 2.3%.[13-17] Several studies have

indicated that screening for HIV is cost-effective when the background rate of undiagnosed infections is greater than 0.1%.[18,19] In the Netherlands, with an overall estimated background rate of HIV infection of 0.2%,[9] HIV screening according to an opt-out policy is already implemented at maternity clinics and sexually transmitted diseases (STD) clinics. The National Institute for Public Health and the Environment (RIVM) also recommends an active test policy, especially in high-risk groups and in patients with HIV indicator conditions such as pneumonia, herpes zoster, seborrhoeic eczema, tuberculosis and hepatitis B and C.[20] The rate of HIV infections in Rotterdam and Amsterdam is, at 0.5 and 0.9% respectively, well above the threshold for testing.

To our knowledge, there is no evidence as to whether non-targeted HIV screening at Dutch EDs is cost-effective. This study is the first to explore HIV prevalence and risk factors for HIV infection at the EDs of three hospitals in the two largest cities in the Netherlands. Additionally, we evaluated whether this approach would be cost-effective.

METHODS

Setting

The cross-sectional multicentre study was performed in two Dutch tertiary referral hospitals: the Erasmus Medical Centre (MC) in Rotterdam and the Academic Medical Centre (AMC) in Amsterdam and one large general hospital, the Sint Franciscus Gasthuis (SFG) in Rotterdam. The participating hospitals are located in two big cities in the Netherlands and provide care for a large inner city population. The ED of the Erasmus MC sees 24,000 patients a year, the AMC 30,000 and the SFG 28,000. All EDs are staffed with emergency physicians, residents and consultants of the different medical disciplines and specialised nurses. The study was conducted between August 2014 and October 2015: eight weeks at the Erasmus MC (18 August 2014 to 16 October 2014), six weeks at the AMC (2 February 2015 to 14 March 2015) and 22 weeks at the SFG (4 May 2015 to 2 October 2015).

Patients

All patients who visited the ED were informed about the study by posters and folders. Patients ≥ 18 years of age who attended the ED and had a blood sample taken for clinical care were eligible and were asked to participate. Patients were included once in case of more than one ED visit during the study period. Patients were included after written informed consent was obtained, as was requested by the medical ethics board. Since an additional blood sample was needed for the study, opt-out testing was not possible. Patients were given the choice to participate, rather than to opt-out, classifying the method as active choice.[21]

We checked patients records and questionnaires (see below) to exclude known HIV positives from blood testing. All study participants at the Erasmus MC and the SFG and a random sample of 100 study participants at the AMC were asked to fill in a questionnaire (in Dutch or in English) covering demographic data and items regarding previous HIV testing, history of STDs, previous HIV indicator conditions such as pneumonia, herpes zoster, seborrhoeic eczema, tuberculosis and hepatitis B and C, (recreational) drug use and perceived risk of HIV transmission. At the Erasmus MC, unused stored blood samples (drawn for diagnostic purposes) of patients of whom no informed consent could be obtained were batch-tested anonymously. These batch-tested samples were not retraceable to patients. The study was approved by the Medical Ethics Board of the Erasmus MC (MEC-2014-205 / NL48384078.14 and MEC-2015-763).

Laboratory HIV test

HIV testing was performed with a third-generation screening ELISA for HIV antibodies combined with an ELISA for the p24 antigen. A positive ELISA test was confirmed with a Western blot. When the ELISA was positive and the Western blot negative, an HIV-RNA PCR was performed. Screening tests were performed in each of the three participating hospitals, confirmation tests for the SFG were performed at the Erasmus MC. An HIV Ag/Ab assay was performed on Liason XL (Diasorin) at the Erasmus MC and the AMC, at the SFG an HIV Ag/Ab assay was performed on the Architect (Abbott).

When a test result was positive, patients were informed by an infectious diseases specialist and were offered linkage to care.

Cost-effectiveness analysis

A Markov model imbedded within a decision tree was created to determine the cost-effectiveness of our HIV screening program (*Appendix, table 1*). The total costs and quality adjusted life years (QALYs) were calculated for two types of patients within the Markov model over a 20-year time horizon: for individuals who never underwent treatment, and for individuals who initiated treatment when the CD4 cell count dropped below 200 cells/µl. Four disease states were included: infected patients with CD4 cell count > 200 cells/µl, with CD4 cell count ≤ 200, infected patients on treatment, and death (*Appendix, figure 1 and table 2*).

We varied the probabilities that someone would test positive at the ED and reported the results for each of these probabilities based on the results of our study. We ranged the probability that an individual would test positive between half of the cases we identified to double the number of cases that we identified. We assumed that the uptake of treatment of those who test positive would

be 99%. All costs and QALYs were discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) below € 20,000 were considered cost-effective in this analysis.[22]

Statistics

Based on the prevalence in other studies we assumed an HIV prevalence of 0.5% at the emergency departments in urban areas. We estimated a number to test of 4000 patients considering a confidence level of alpha = 0.05 and a power of 0.80. Analysis was performed with SPSS (IBM SPSS Statistics 21).

RESULTS

HIV prevalence

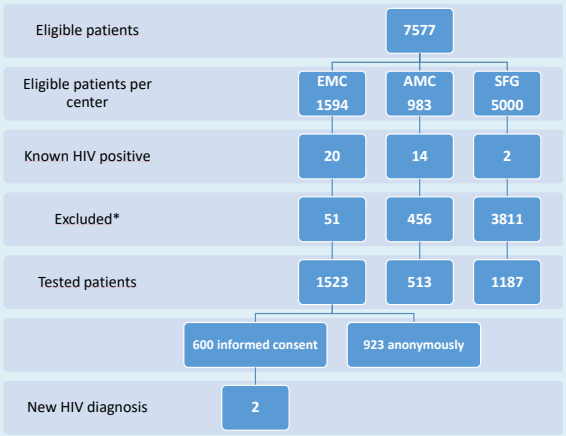
A total of 7577 patients were eligible during the study period and 3223 patients were tested, resulting in an inclusion rate of 43% (*figure 1*). At the Erasmus MC 600 of 1594 eligible patients consented to participate in the study (38%), at the AMC 513 of 983 eligible patients (52%) and at the SFG 1187 of 5000 (24%). Reasons for not participating were, amongst others, not being able to give consent, language barrier, forgotten to ask, patient leaving the ED before being asked and/or patient attending the ED more than once during the study period. The baseline characteristics are shown in *table 1*. The median age was 57 years and slightly more males than females were included. The majority of patients were of Dutch origin. First-generation immigrants predominantly originated from Surinam and the Caribbean and other European countries.

Two patients (0.06%) were newly diagnosed with an HIV infection, both in the Erasmus MC, and 36 patients were already known to be HIV infected and under the care in an HIV treatment centre. A total of 923 participants from the Erasmus MC, without informed consent, were tested anonymously and none tested HIV positive.

At the Erasmus MC and the AMC the percentage of HIV-infected patients seen at the ED (1.38% (22/1594), including the two newly diagnosed) and 1.42% (14/983)) respectively was comparable. At the SFG 0.04% (2/5000) of patients attending the ED were known to be HIV positive.

Of all patients visiting the ED who filled in a questionnaire, 2% reported a perceived risk for HIV transmission and almost 20% of all patients reported previous HIV testing (*table 2*). Reported illicit drug use was low (3% of the population) and intravenous drug use was not reported at all. Symptoms of fatigue and/or weight loss were present in 41% of patients and 29% of patients reported having had an HIV-indicator condition at any time. Most frequently reported HIV-indicator conditions were pneumonia and herpes zoster. If we had only tested patients with one or more risk factor, the HIV prevalence would have been nearly 0.2% (2 out of 1151 reported risk factors).

Figure 1. *Patients included in the study*



*Not being able to give consent, language barrier, forgotten to ask, patient leaving the ED before being asked, patient attending the ED more than once during the study period, no extra blood sample available, no result.

Characteristics of newly diagnosed patients

The two newly diagnosed HIV-infected patients were both heterosexual, older, male patients of non-Dutch origin, who had never had an HIV test. The first, a 50-year-old Cape Verdean, presented with a minor head injury, walking difficulties and bradyphrenia. His medical history was remarkable for pulmonary tuberculosis in 2006 and herpes zoster infection in 2013. The CD4 cell count at presentation was 170 cells per µl. After the HIV diagnosis, his cognitive dysfunction was thought to be secondary to HIV encephalitis/dementia based on MRI and lumbar puncture results and antiretroviral therapy was started. The second patient, a 73-year-old man from Spain, presented with cognitive dysfunction, hyponatraemia, leukopenia, and thrombocytopenia. His medical history was remarkable for syphilis in 1984 and 1995; in 2003 he was lost to follow-up during analysis for neurosyphilis. In 2013 and 2014 he was diagnosed with herpes zoster. The CD4 cell count at presentation was 80 cells per µl. Cerebral MRI showed atrophy and white matter abnormalities, a lumbar puncture was negative for HIV virus, syphilis and JC virus, and antiretroviral therapy was started.

Cost-effectiveness analysis

Non-targeted HIV testing at the ED is not cost-effective. Our study, where two patients out of 3223 participants tested positive, led to an ICER of € 77,050 per QALY gained, more than triple the current Dutch threshold for cost-effectiveness. If four patients had tested positive, the

Table 1. *Characteristics of patients included in the study*

Tested per centre	EMC N = 1523	AMC N = 513	SFG N = 1187	Total N = 3223
Informed consent, N	600	513	1187	2300
Tested anonymously, N	923	0	0	923
Age, years (median; 25th -75th percentile)	56 (42-66)	57 (43-70)	58 (43-72)	57 (42-70)
Female sex, %	40	44	53	47
Questionnaire filled in	418 (70)	98 (19)	879 (74)	1395 (60)
Nationality as reported in questionnaire				
Born in the Netherlands	326 (78)	75 (77)	709 (81)	1110 (80)
- Both parents Dutch	288 (88)	65 (87)	633 (89)	986 (89)
- One or both parents born abroad	38 (12)	10 (13)	76 (11)	124 (11)
Immigrants	92 (22)	23 (23)	166 (19)	281 (20)
- Sub Saharan African	7 (8)	2 (9)	9 (5)	18 (6)
- Moroccan	10 (11)	0	14 (8)	24 (9)
- Surinam and Caribbean	36 (39)	13 (57)	44 (27)	93 (33)
- Turkish	7 (8)	0	18 (11)	25 (9)
- Asian (except from Turkey)	11 (12)	3 (13)	19 (11)	33 (12)
- Other Europeans#	16 (17)	2 (9)	26 (16)	44 (16)
- Others##	5 (5)	3 (13)	36 (22)	44 (16)

Numbers are N (%) unless otherwise indicated
EMC = Erasmus Medical Centre; AMC = Academic Medical Centre; SFG = Sint Franciscus Gasthuis
#: Austria (N=1), Belgium (N=3), Bosnia (N=1), Croatia (N=2), Germany (N=7), Greece (N=2), France (N=1), Hungary (N=2), Ireland (N=1), Italy (N=4), Latvia (N=1), Lithuania (N=1), Macedonia (N=1), Norway (N=1), Poland (N=4), Portugal (N=4), Scotland (N=1), Serbia (N=2), Slovakia (N=1), Spain (N=2), Yugoslavia (N=2)
other: Australia (N=1), Colombia (N=1), Egypt (N=3), Guyana (N=2), Mauretania (N=1), Mexico (N=1), Montserrat (N=1), Nicaragua (N=1), Tunisia (N=1) not specified (N=31).

ICER would have decreased to € 70,032 per QALY gained. If just one patient had tested positive, testing at the ED would become far less cost-effective at € 91,084 per QALY gained. Even if testing had been targeted to those who are demographically more likely to test positive (i.e. only men over the age of 45 years and of non-Dutch origin, like the two newly HIV-diagnosed patients), the ICERs would have remained above € 60,000 per QALY gained (*Appendix, table 3*).

DISCUSSION

We showed that it was feasible to achieve an uptake of 40-50% of non-targeted HIV testing in two tertiary referral hospitals and one general hospital in the two largest cities of the Netherlands. The HIV prevalence in the population is 0.5% in Rotterdam and 0.9% in Amsterdam and the estimated HIV prevalence among undiagnosed persons 0.21% and 0.12% respectively.[9] In our study, however, only two patients were newly diagnosed with an HIV infection (0.06%). Both patients were at risk for HIV infection and targeted or diagnostic HIV testing could have been performed at an earlier stage. The non-targeted HIV testing at the ED was not cost-effective at more than three times the current threshold for cost-effectiveness, which suggests that targeted screening programs to those with identifiable risk factors may be more effective.[23]

In our study, patients were offered HIV testing and had an active choice to participate rather than to opt-out. The inclusion rate was 43%. In a randomised clinical trial, inclusion of patients in an opt-out strategy was 66%, nearly 15% higher than in an active choice strategy (51%).[21] The prevalence of HIV infection that we found in patients visiting the ED is in line with other studies, but the percentage of newly diagnosed patients with HIV infections (0.06%) was lower.[13-17,23] In studies from the USA and France percentages of 0.52%, (range 0.14-1.7%) have been reported,[23] 0.08% in Ireland,[24] 0.14% in France[25] and 0.4% in Spain.[26]
Our low percentage of new HIV infections may be due to the various intervention strategies already implemented

Table 2. *Reported risk factors for having HIV infection*

	EMC N = 600	AMC N = 513	SFG N = 1187	Total N = 2300
Questionnaire filled in	418 (70)	98 (19)	879 (74)	1395 (60)
Drug abuse+	12 (3)	3 (3)	31 (4)	46 (3)
Fatigue/weight loss	199 (48)	43 (44)	331 (38)	573 (41)
Indicator illness (except Hepatitis/STD)	138 (33)	31 (32)	237 (27)	406 (29)
- Pneumonia	72 (52)	21 (68)	113 (48)	206 (51)
- Herpes zoster	25 (18)	8 (26)	50 (21)	83 (20)
- Seborrhoeic eczema	5 (4)	0	17 (7)	22 (5)
- Tuberculosis	10 (7)	1 (3)	8 (3)	19 (5)
- Multiple	17 (12)	0	23 (10)	40 (10)
- Not specified	9 (7)	1 (3)	26 (11)	36 (9)
Hepatitis B or C	14 (3)	2 (2)	10 (1)	26 (2)
STD	34 (8)	5 (5)	61 (7)	100 (7)
Previous HIV test (self-reported)	92 (22)	27 (28)	146 (17)	265 (19)
Perceived HIV risk	12 (3)	2 (2)	18 (2)	32 (2)

Numbers are N(%) unless otherwise indicated.
EMC = Erasmus Medical Centre; AMC = Academic Medical Centre; SFG = Sint Franciscus Gasthuis
+: Subdivided in multiple drugs, heroin iv, heroin not iv, cocaine/crack, marihuana, XTC/amphetamines, GHB, others. Data not shown because of small numbers.

to increase testing rates in the Netherlands, such as opt-out screening among pregnant women and in STD clinics with an uptake of more than 99%, guidelines for repeated HIV testing of men who have sex with men (MSM),[27] as well as internet facilities for HIV testing and partner notification.[9] Since it is not clear what preventive strategies are implemented in the settings in which the non-targeted HIV testing studies were performed, results of studies cannot be easily compared. The same holds true for the heterogeneity of patient populations and how the screening was implemented.[21] Hsieh et al. showed that HIV infections are more prevalent among patients who were not offered or declined HIV testing compared with those who opted-in.[15] However, in our study, HIV prevalence in the group in which no informed consent could be obtained (the 923 patients in the Erasmus MC tested anonymously), was not higher than in those who opted-in.

Another reason for the low prevalence of undiagnosed HIV infections in this study could be that the ED population is not representative of the inner city population. In the two tertiary referral hospitals a large percentage of patients are living in rural areas and predominantly of Dutch origin.

Implementation of non-targeted screening is difficult.[28-30] Barriers towards implementation and sustainability include costs, the effect on patients' length of stay at the ED, and staff to perform testing and deliver results.[31-33] Therefore, targeted test strategies aimed at patients with identifiable risk factors have been evaluated in the USA, the UK and Spain. Two studies showed that targeted testing was associated with identification of more new HIV infections when compared with non-targeted testing,[26,30] whereas another study failed to demonstrate this benefit.[34] In our study, 3% of the patients migrated from an HIV endemic area, 29% reported having had an indicator disease and only 2% of the patients indicated that they perceived having a risk for HIV transmission. Indeed, both of the newly diagnosed HIV patients belonged to the high HIV risk group of migrants from a country with a high prevalence of HIV or having had multiple sexually transmitted diseases.

The cost-effectiveness analysis based on the identification of the two patients with HIV infection resulted in an ICER of € 77,050 per QALY gained. It is likely that testing for HIV in the ED is even less cost-effective than we found in our study. We assumed that patients who are not tested at the ED will never test positive and die without a diagnosis. It is likely, however, that these patients would have presented and subsequently tested positive before death, making HIV screening at the ED even less cost-effective. As it is unknown what would have happened

to these patients if they had not been diagnosed, we have chosen to compare them to the worst case scenario of death without diagnosis. Taking HIV transmission into account, in the UK annual HIV testing of all adults was calculated to cost £ 67,000 - £ 106,000/QALY gained, assuming that 25% of people living with HIV are undiagnosed.[35] Thus, it seems that non-targeted HIV testing will only be nearing cost-effectiveness when the prevalence in the population is high or the percentage of undiagnosed people living with HIV is much higher than the 12-34% in the Netherlands. Of note, if annual testing was only offered to MSM, patients with intravenous drug use and people from HIV-endemic countries, with one-time testing for all other adults, then the costs would be £ 17,500/QALY gained,[35] again suggesting targeted testing is preferable from a cost-effectiveness point of view. All studies suggest that to identify a few newly diagnosed patients, thousands of patients need to be screened.[23]

Our study has a number of limitations. First, we were not able to estimate the exact refusal and incidence rates, since patients not consenting consisted of patients not being offered the test at the ED, patients being not able to consent and patients refusing the test. It is also possible that the exclusion of these patients may have influenced the HIV prevalence, but our inclusion percentage is higher than in many other studies.[23,32,33,36] Moreover, we did not find additional HIV infections in the 923 patients who were anonymously tested after failing to consent to the study. Second, due to practical problems and financial constraints, the inclusion procedure, the use of the questionnaire and anonymous testing of non-participants differed between the participating hospitals. It is unlikely that this influenced the outcome of this study, as positive test results were very low in all groups.
Due to the same reasons as mentioned above we did not succeed in inclusion of the calculated number of patients needed. Finally we did not get feedback about the acceptability of HIV testing in this setting.

CONCLUSION

In conclusion, non-targeted HIV testing in two urban areas in the Netherlands had a low yield of new HIV infections and was not cost-effective. Our data suggest that targeted HIV testing may offer an alternative approach to decrease the number of not yet diagnosed people living with HIV. According to the recommendations by the RIVM we suggest HIV testing in people presenting at the ED with an HIV indicator disease (pneumonia, herpes zoster, seborrhoeic eczema, tuberculosis and hepatitis B and C or STD), especially in patients from high-risk groups (MSM, immigrants and illegal drug users).

DISCLOSURES

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APPENDIX

Figure 1. *Markov states*

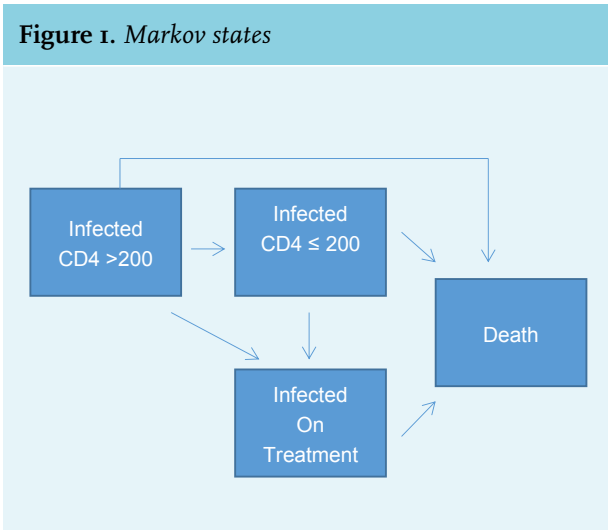

Table 1. *Markov state yearly transition probabilities for the two evaluated scenarios: when an HIV-infected individual never initiates treatment, and when an HIV-infected individual initiates treatment with a CD4 cell count ≤ 200 cells/μl*

Transition Probabilities					
From	**To**	**Transition Probability: Never going on treatment**	**Source**	**Transition Probability: Going on treatment with CD4 cell count ≤ 200**	**Source**
Infected, CD4 > 200 cells/μl	Infected, CD4 >200 cells/μl	0.858	[37]	0.858	[37]
Infected, CD4 > 200 cells/μl	Infected, CD4 ≤200 cells/μl	0.118	[37]	0.118	[37]
Infected, CD4 > 200 cells/μl	Infected, on treatment	0	Assumption	0	Assumption
Infected, CD4 > 200 cells/μl	Death	0.025	[5,38,39]	0.025	[5,38,39]
Infected, CD4 ≤ 200 cells/μl	Infected, CD4 ≤200 cells/μl	0.5	[37]	0.48	[37]
Infected, CD4 ≤ 200 cells/μl	Infected, on treatment	0	Assumption	0.48	Data from this study
Infected, CD4 ≤ 200 cells/μl	Death	0.5	[5,38,39]	0.04	[5,38,39]
Infected, on treatment	Infected, on treatment	0	Assumption	0.97	Assumption
Infected, on treatment	Death	0	Assumption	0.03	[5,38,39]

Table 2. *Costs and quality adjusted life years*

State	Cost	Source
Infected, CD4 > 200 cells/μl	€ 1746*	[10], Local data
Infected, CD4 ≤ 200 cells/μl	€ 6365*	[10], Local data
Infected, on treatment	€ 12,987**	[40], Local data
Cost of HIV testing	€ 20	[40], Local data
Utility Weight		
Infected, CD4 > 200 cells/μl	0.88	[41]
Infected, CD4 ≤ 200 cells/μl	0.7	[41]
Infected, on treatment	0.94	[41]
Death	0	[42]

*Non-ART direct medical costs associated with different HIV disease states. Estimated from Dutch HIV Monitoring Data

Table 3. *Results of cost-effectiveness analysis: based on the probability and uncertainty of testing positive for HIV at the emergency department*

Testing scenario	Probability of testing positive	Cost-effectiveness ratio of testing at the emergency department versus not testing
Test all ED patients	0.0006 (0.0012-0.0003)	€ 77,050 (€ 70,032 -€ 91,084)*
Only test males in ED	0.001 (0.002-0.0005)	€ 70,445 (€ 66,730 - € 77,876)*
Only test non-Dutch patients in ED	0.004 (0.007-0.002)	€ 65,421 (€ 64,218 - € 67,826)*

*Ranges correspond to the ranges in the probabilities

ORIGINAL ARTICLE

Helicobacter pylori resistance in the Netherlands: a growing problem?

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ABSTRACT

Helicobacter pylori infection is clinically associated with dyspepsia, gastric and duodenal ulcers, and gastric cancer. Increasing antimicrobial resistance in *H. pylori* is a worldwide problem and failure of eradication with standard triple therapy (high-dose proton pump inhibition, amoxicillin and clarithromycin) is directly related to the presence of a resistant strain. Other treatment combinations have been investigated, but with inconsistent results. Based on a review of the recent literature in conjunction with an analysis of the regional resistance data, we address the increasing complexity of *H. pylori* eradication therapy. Culture and susceptibility results of all first *H. pylori* isolates of adults (> 18 years) seen in the Leiden University Medical Center, from January 2006 to December 2015, were analysed (n = 707). An increase in clarithromycin resistance was observed from 9.8% to 18.1% (p = 0.002) in the periods from 2006-2010 and 2011-2015, respectively. For ampicillin the resistance increased from 6.3% to 10.0% (p = 0.37), and for metronidazole from 20.7% to 23.2% (p = 0.42). The tetracycline resistance remained low at 3.2% and 2.3%, respectively. The treatment paradigm is shifting towards individualised treatment rather than a one-strategy-fits-all approach. In case of treatment failure it should be strongly considered to refer a patient for endoscopy, biopsy and culture. Thereafter, targeted antimicrobial treatment based on susceptibility results can be initiated. Furthermore, accumulating data indicate that prolongation of treatment to 14 days, as opposed to the current standard 7 day course, contributes to a higher *H. pylori* eradication rate.

KEYWORDS

Helicobacter pylori, resistance, antibiotic stewardship, treatment.

INTRODUCTION

Helicobacter pylori is a curved, sometimes spiral, Gram-negative rod-shaped bacterium which has its niche in the gastric epithelium. Because of the production of urease and the presence of flagella, *H. pylori* is able to survive in this highly acidic environment. Robin Warren and Barry Marshall first isolated *H. pylori* in Australia in 1982. In 1985, Marshall fulfilled the postulates of Koch by infecting himself with the bacterium and in 2005 he (along with Warren) received the Nobel Prize for Medicine for demonstrating the causal link between *H. pylori* and peptic ulcers. In addition, *H. pylori* has been associated with dyspepsia and gastric cancer as well as with a number of other diseases including idiopathic thrombocytopenic purpura and iron deficiency anaemia.[1] Approximately 50% of the world population is infected with *H. pylori*, but there is a large geographic variation. In the majority of people the infection is asymptomatic. In northern Europe and North America the average prevalence of 'carriership' (or asymptomatic infection) is approximately 30%, while in low-income countries this percentage may exceed 70%.[2] The prevalence of *H. pylori* has shown a decline in developed countries over time. However, given its widespread dissemination and its potential to cause disease, recent observations that antimicrobial resistance of *H. pylori* is rapidly increasing may – eventually – have substantial effects on human health.[3-5] It is known that the antibiotic resistance of *H. pylori* varies by region, for example in the UK the resistance to clarithromycin is reported to be < 10%, while in Turkey it is > 40%.[2] Already as a result, failure of standard triple therapy with high-dose proton pump inhibition, amoxicillin and clarithromycin is increasing.[2] Many other treatment combinations have been investigated, but trials and cohort studies showed inconsistent or incomparable results.[6]

Several barriers hinder the optimisation of targeted antimicrobial treatment based on susceptibility patterns,

which is usual for other pathogens. An invasive endoscopic procedure including gastric and/or duodenal biopsies is needed for adequate samples for cultivation of *H. pylori*. Due to the fastidious nature of *H. pylori* these biopsies need to arrive at the laboratory within hours. Furthermore, *H. pylori* grows slowly and requires specific culture conditions such as an optimal medium, correct temperature and pH, as well as a microaerophilic atmosphere (i.e. lower amounts of oxygen: 5-10%). If the laboratory is capable of assessment of susceptibility patterns, agents tested usually include ampicillin (amoxicillin), clarithromycin, levofloxacin, metronidazole, rifampicin, and tetracycline.[7] The presence of *H. pylori* can also easily and reliably be detected with cheaper, non-invasive techniques, e.g. faecal antigen tests. These are effective in settings of low prevalence of resistance.[8,9] However, the use of non-invasive techniques for *H. pylori* detection, which do not deliver information about susceptibility patterns, will contribute to a further increase in resistance and treatment failure rates in settings with a higher a priori risk for *H. pylori* resistance. Hence, internationally, the treatment paradigm is now shifting towards individualised medicine.[4]

In the Netherlands, only a few laboratories routinely conduct resistance testing of *H. pylori*, and resistance data for *H. pylori* are not reported in the Dutch annual national resistance report (Nethmap[10]). At present, a lack of data precludes sufficient insight into the epidemiology of antimicrobial resistance of *H. pylori* in the Netherlands. Based on description of loco-regional resistance data we address the increasingly complex issue of optimising antimicrobial treatment of *H. pylori* infection in the Netherlands.

METHODS

Study population

In the Leiden University Medical Center biopsies for *H. pylori* culture are routinely performed when there is a suspicion of *H. pylori* infection in the anamnesis or when performing the gastroscopy. Two biopsies in the antrum and two biopsies in the corpus are sent in for culture. Culture and susceptibility results of all first *H. pylori* isolates of adults (> 18 years) from January 2006 to December 2015, were obtained from the database of the Department of Medical Microbiology. In addition, the surname of the patient was retrieved to discriminate between patients from autochthonous or foreign descent. Since no intervention was performed and data were anonymised prior to the final analysis, it was not necessary to obtain informed consent.

Microbiology methods

All gastric or duodenal biopsies arrived at the laboratory within several hours. Biopsies arrived in tubes with 2 ml of physiological salt 0.85% (Media Products, Groningen, the Netherlands). Cultures were incubated in microaerophilic conditions at 35°C on nonselective Columbia agar with 5% sheep blood and selective Pylori agar (bioMerieux Benelux B.V., Boxtel, the Netherlands). *Campylobacter jejuni* ATCC 29428 was used as a growth control and cultures were evaluated on days 3-5 and day 7 (*figure 1*). In case of a positive culture, further determination was performed by Gram stain and oxidase, catalase and urea tests.

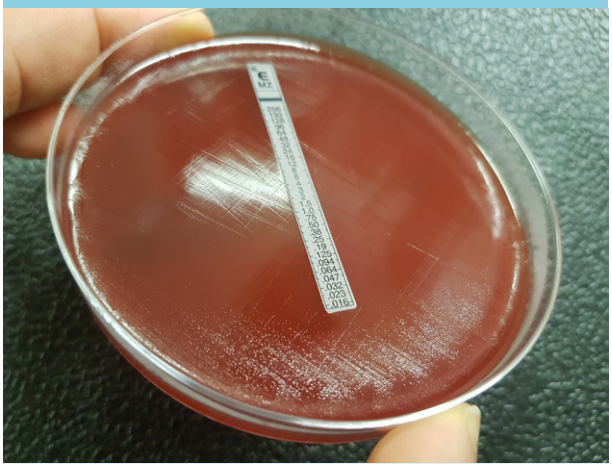
Susceptibilities were determined for ampicillin, clarithromycin, levofloxacin, metronidazole, rifampicin, and tetracycline. A McFarland 3 suspension was incubated microaerophilically on Brain Heart Infusion agar (Media Products, Groningen, the Netherlands) at 35°C for 3-5 days. The minimum inhibitory concentration values, i.e. the lowest concentration of an antibiotic that prevents visible growth of a bacterium, were determined by Etest (AB Biodisk, Solna, Sweden) and categorised into sensitive (S), intermediate (I) or resistant (R) for the respective antibiotic based on the 'European Committee on Antimicrobial Susceptibility Testing' breakpoint tables (*figure 2*).[6]

Statistical analyses

Resistance rates for antimicrobial agents commonly used to treat *H. pylori* infection were compared by Chi-square tests between the periods 2006-2010 and 2011-2015. Data are presented as numbers and percentages for each antibiotic separately. To estimate influence of selection

Figure 1. *Microaerophilic incubation of* H. pylori *cultures and the* Campylobacter jejuni *ATCC 29428 as growth control by the Anoxomat (Mart Microbiology, Drachten, the Netherlands)*

Figure 2. *Growth of a* H. pylori *strain that is susceptible to metronidazole with a minimum inhibitory concentration of 0.016 mg/l as determined by Etest*



bias, in particular by receiving an indication for gastric endoscopy due to failed treatment courses for *H. pylori,* a random sample of approximately 5% was drawn from the original dataset to verify pre-treatment. Effect modification was verified by adding an interaction term to the model. The IBM SPSS statistical software package (version 23) was used to perform all calculations.

RESULTS

In the period from 2006-2015, *H. pylori* strains were isolated from a cohort of 707 adult patients. The number of isolates per year varied from 50 to 94, but did not show a rising trend over the years (linear-by-linear association test p = 0.46). The mean age of the patient at the moment of biopsy was 55 years (SD 15 years), approximately half were female (n = 369, 52.2%). The main reason for gastroscopy was dyspepsia (n = 197, 27.9%), pain in the epigastric region (n = 59, 8.3%), dysphagia (n = 46, 6.5%) or other stomach complaints (n = 69, 9.8%). Almost 12% of the gastroscopic procedures were performed to assess the aetiology of gastrointestinal bleeding (n = 44, 6.8%) or to assess the presence of varices (n=35, 5.0%). Gastroscopies were also performed in the work-up of analyses of anaemia (n = 104, 14.7%) or weight loss (n = 51, 7.2%). Only in 19 patients was the determination of *H. pylori* resistance the indication for gastroscopy (2.7%). The indication for gastroscopy was assessed as 'other' in 43 cases (6.0%) and could not be retrieved in 40 cases (5.7%). The percentage of successful determination of the antibiotic resistance percentage was about 90%. The proportion of isolates from Dutch vs. other ethnic backgrounds was stable over the years (mean 39%, range 29-48%).

For clarithromycin an increase in resistance was observed from 9.8% to 18.1% (p = 0.002) in the periods from 2006-2010 and 2011-2015, respectively (*table 1*). Resistance between these periods also increased for ampicillin from 6.3% to 10.0% (p = 0.37), and metronidazole from 20.7% to 23.2% (p = 0.42). In the case of tetracycline, resistance remained low at 3.2% and 2.3%, respectively. For levofloxacin, resistance was only assessed from 2013 onwards. There was no effect modification by ethnic background of the increase in resistance of *H. pylori* (p-value for interaction > 0.10). In our sample of pre-treatment verification, pre-treatment of *H. pylori* was only documented in one of 45 patients (2%).

Table 1. *Resistance rates of H. pylori to specific antibiotics in the Leiden University Medical Center over the period 2006-2015*

Time period	2006 – 2010			2011 – 2015			
Antibiotic	**Total number of cultures**	**Number of I or R cultures**	**Percentage of I or R cultures**	**Total number of cultures**	**Number of I or R cultures**	**Percentage of I or R cultures**	**p-value**
Clarithromycin	357	35	9.8	336	61	18.1	0.002
Metronidazole	352	73	20.7	335	78	23.2	0.421
Ampicillin	63	4	6.3	209	21	10.0	0.373
Levofloxacin	n.a.	n.a.	n.a.	185	24	13.0	n.a.
Tetracycline	63	2	3.2	219	5	2.3	0.689
Rifampicin	n.a.	n.a.	n.a.	190	84	44.2	n.a.

Culture results for *Helicobacter pylori* with values intermediate (I) or resistant (R) for the respective antibiotic are based on the European Committee on Antimicrobial Susceptibility Testing breakpoint tables.[7] n.a = not available.

DISCUSSION

We found an increase in the average antimicrobial resistance rates of *H. pylori*, in particular for clarithromycin, over the last ten years. This finding does not appear to be mitigated by an increase in the proportion of non-autochthonous patients or selection of pre-treated patients. However, it cannot be completely excluded that in the general population or, for example, in a different geographic location in the Netherlands, resistance rates are lower and/or stable.[11] It is expected that the effectiveness of triple therapy will decrease as a result of increasing clarithromycin and amoxicillin resistance.[2] When clarithromycin resistance is present, the chances of successful treatment decrease from 90% to 44%.[6] With increasing resistance, the standard regimen might actually be monotherapy with either amoxicillin or clarithromycin. This creates a negative spiral, which increases the resistance of *H. pylori* for both these drugs.

Future directions: choice of antimicrobials and duration of treatment

In the Netherlands, the standard policy according to the general practitioner guideline is triple therapy: proton pump inhibition, amoxicillin (2 dd 1000 mg) and clarithromycin (2 dd 500 mg) each orally for 7 days.[8,9] If therapy is not successful, the current Dutch general practitioner guidelines recommend a second course of proton pump inhibition, amoxicillin (2 dd 1000 mg) and metronidazole (2 dd 500 mg) for 7 days without performance of any further diagnostic tests.[8,9]

In a recently published network meta-analysis different therapies for *H. pylori* were compared with regard to efficacy and side effects.[6] A network meta-analysis pools studies in order to compare treatments which have not previously been directly compared with each other. In the current network meta-analysis 14 therapies in 143 studies were compared and ranked in terms of effectiveness (n = 32,056 patients) and adverse effects profile (n = 22,180 patients). The standard triple therapy showed to be the second least effective therapy; only a 7-day regimen based on levofloxacin performed worse. Furthermore, the analyses indicated that a longer duration of therapy was more effective, but also accompanied by more side effects. A major drawback of this study is that local resistance figures were not taken into account.[4]

Recently a consensus statement, based on the opinions of experts in the field, recommended first-line therapy with clarithromycin and either amoxicillin or metronidazole in regions where there is low probability (< 15%) of resistance for clarithromycin.[3] In regions with high resistance rates (> 15%) against clarithromycin, quadruple therapy is advised: non-bismuth based (amoxicillin, metronidazole and clarithromycin) or bismuth based (bismuth, metronidazole, tetracycline).[3] Noteworthy, in the Netherlands, bismuth is still hard to obtain. Another option suggested in the consensus statement is a levofloxacin-containing triple therapy. The consensus additionally recommended to extend the treatment duration of *H. pylori* to 14 days.[3]

CONCLUSION

Approximately 50% of the worldwide population are *H. pylori* carriers. *H. pylori* can cause dyspepsia, ulcers and gastric cancer. Our regional data suggest that *H. pylori* resistance is an increasing problem in the Netherlands. Based on these resistance data, the recommended standard 7-day triple therapy with high-dose proton pump inhibition, amoxicillin and clarithromycin is not always the best choice. Over time, resistance may further develop as a major cause of therapy failure. Therefore local resistance data should be taken into account when deciding about the optimal diagnostic and therapeutic strategy. In case of treatment failure, it should be strongly considered to refer a patient for endoscopy, biopsy and culture. When a second treatment based on the susceptibility pattern is prescribed, a longer duration of treatment (14 days instead of 7 days) probably contributes to a greater success rate. In addition, systematic monitoring of the development of antimicrobial resistance of *H. pylori* in the Netherlands seems appropriate.

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DISCLOSURES

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ORIGINAL ARTICLE

Unfavourable blood pressure and LDL-cholesterol levels in obese non-diabetic individuals

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ABSTRACT

Background: Early diagnosis and treatment of high blood pressure (BP) and cholesterol is important to reduce cardiovascular risk. We compared BP and LDL-cholesterol (LDL-C) as well as the quality of treatment between obese subjects and normal weight and overweight individuals.
Methods: 87,648 participants of the Lifelines study were categorised according to obesity (normal weight/overweight/obesity) and age. Mean systolic BP and LDL-C were calculated depending on treatment, BMI, age and sex.
Results: In all age groups, except those aged 70-80 years, women had a significantly lower BP than men. Use of BP-lowering medication did not result in BP levels comparable with non-users, except in those aged 70-80 years. Despite medication, the BP was insufficiently controlled in 20-50% of participants. BP was significantly higher in obese vs. normal weight and overweight individuals of all ages, but most apparently in men younger than 50 years. Mean LDL-C varied between 2.5-3.0 mmol/l. Despite higher statin use, obese participants had a higher LDL-C than those with a normal weight. Statins abolished the age-dependent LDL-C increase. Many participants did not achieve target LDL-C < 2.5 mmol/l. A small percentage of individuals treated with BP-lowering drugs were also using statins (overall 32% in men, 17% in women).
Conclusion: Obese individuals, especially men younger than 50, have a higher BP and LDL-C compared with those with overweight and a normal weight. Use of BP-lowering drugs did not revert the BP back to levels normal for the specific age and BMI group, whereas statins abolished the age-related increase in LDL-C. These data suggest that more attention is needed for active screening and treatment of cardiovascular risk factors.

KEYWORDS

Blood pressure, lipids, obesity, epidemiology, treatment

INTRODUCTION

Several long-term follow-up studies have shown that cardiovascular risk gradually increases with increasing levels of blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C).[1-3] Current risk engines and guidelines give specific estimates of excess of risk related to these risk factors.[4-8] They also describe target levels for BP and LDL-C above which pharmacotherapy should be started or intensified.
As the BP rises with increasing age, setting a specific target level for treatment may be appropriate for a younger age group, but too aggressive for an elderly age group. Indeed, there may be considerable side effects of aggressive BP-lowering treatment in the elderly.[9,10] In the Joint National Committee (JNC) 8 treatment guideline for hypertension, it was advised to aim for a BP < 140/90 mmHg in non-diabetic adults (< 60 years), whereas BP values < 150/90 mmHg were advised for elderly people (≥ 60 years). However, the recent SPRINT study suggested that a systolic BP in the 125-135 mmHg range is probably the optimal target for most hypertensive patients.[11]
Elevated LDL-C levels have been identified as another major factor contributing to cardiovascular disease (CVD). A multitude of randomised clinical trials have shown that cholesterol lowering with statin therapy reduces cardiovascular morbidity and mortality.[12,13] The 2011 ESC/EAS Guidelines for the management of dyslipidaemias

proposed an LDL-C treatment target of < 2.5 mmol/l for subjects at high risk, while for subjects at moderate risk, an LDL-C target of < 3.0 mmol/l could be considered.[5]

Obesity is a major contributor to the global burden of chronic diseases and disabilities.[14,15] Increased adiposity is a key risk factor for hypertension, dyslipidaemia, type 2 diabetes and cardiovascular disease. Previously, we have shown that elevated BP ≥ 140 mmHg was present in 45-70% of obese individuals in an international multi-cohort study.[15] In the NHANES study, prevalence of hypertension and dyslipidaemia was the highest in obese participants compared with overweight and non-obese individuals.[16]

Several studies have reported on the quality of BP and lipid control in several distinct populations,[17-18] as well as measures to enhance medication adherence.[19] In 2014, data from NHANES showed that untreated hypertension had decreased among obese and overweight adults and untreated dyslipidaemia had decreased for all weight groups.[16] The recent EUROASPIRE IV survey showed, however, that large proportions of patients at high CVD risk have insufficiently controlled BP and lipids.[20] Other recent papers have suggested a degree of clinical inertia in treating high BP, especially in the context of obesity.[21,22]

In this paper we report cross-sectional data on levels of BP and LDL-C, and treatment of these risk factors in participants of the Lifelines Cohort Study, a prospective population-based study in the Netherlands. The analysis is part of a 'Healthy Obesity' research program.[15] The main question we aimed to answer was whether there were differences in the cardiovascular risk factor levels of BP and LDL-C for obese subjects within different age cohorts compared with those with normal weight and overweight. Also, we wanted to assess the quality of single and combined treatment of BP and LDL-C in these subjects.

MATERIALS AND METHODS

Subjects

In this cross-sectional study, we used data from subjects participating in the Lifelines Cohort Study. Lifelines is a multi-disciplinary prospective population-based cohort study examining, in a unique three-generation design, the health and health-related behaviours of persons living in the north of the Netherlands. It started in 2007, and employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The methodology has been described previously.[23,24] All participants were between 18 and 90 years at the time of enrolment. They provided written informed consent before participating in the study. The study protocol was approved by the medical ethics review committee of the University Medical Center Groningen. In the present study, we included subjects with an age between 18 and 80 years, who were of Western European descent, did not have diabetes mellitus, and who participated between 2007 and 2013.

Clinical examination and definitions

Subjects completed a self-administered questionnaire on medical history, past and current diseases, use of medication and health behaviour at home. Medication use was verified by a certified research assistant, and scored by the Anatomical Therapeutic Chemical (ATC) Classification System, a system developed for the classification of active ingredients of drugs. The number of different medications used by a participant was considered a proxy for multimorbidity.[25] Diagnosis of type 2 diabetes mellitus was based either on self-report (known diabetes), or on the finding of a single measurement of fasting blood glucose ≥ 7.0 mmol/l at Lifelines' screening (newly-diagnosed diabetes). Smoking status was defined as non-smoker, former smoker and current smoker (including the use of cigarettes, cigarillos, cigars and pipe tobacco).

A standardised protocol was used to obtain BP and anthropometric measurements: height, weight, and waist circumference. BP was measured every minute during a period of 10 minutes with an automated DINAMAP Monitor (GE Healthcare, Freiburg, Germany). The size of the cuff was chosen according to the arm circumference of the participant. The average of the final three readings was recorded for systolic and diastolic BP. Because of the great interest for systolic BP control in the prevention of CVD, in this paper we focus on systolic BP only. Heart rate was measured simultaneously with the BP. Anthropometric measurements were done with the participant in light clothing and without shoes. Body weight was measured to the nearest 0.1 kg. Height and waist circumference were measured to the nearest 0.5 cm. Waist circumference was measured in standing position with a tape measure all around the body, midway between the lower rib margin and the iliac crest. Body weight and height were used to calculate body mass index (BMI) (weight (kg)/height $(m)^2$), which was categorised as normal weight (18-25 kg/m^2), overweight (25-30 kg/m^2) and obesity (≥ 30 kg/m^2). As many of the Lifelines participants are treated solely by their general practitioner, we applied the target and cut-off values for high BP (< 140 mmHg) and elevated LDL-C (< 2.5 mmol/l) valid in 2013.

Biochemical measurements

Blood samples were collected in the morning after an overnight fast, directly into tubes containing heparin, and centrifuged. Serum levels of total and HDL cholesterol

were measured using an enzymatic colorimetric method, triglycerides using a colorimetric UV method, and LDL-C using an enzymatic method, all on a Roche Modular P chemistry analyser (Roche, Basel, Switzerland). Serum creatinine was measured on a Roche Modular P chemistry analyser (Roche, Basel, Switzerland). Fasting blood glucose was measured using a hexokinase method.

Calculations and statistical analysis

BP and LDL-C are reported in subgroups that were defined by sex, BMI (normal weight, overweight and obese) and age groups (18-30 years, 30-40 years, 40-50 years, 50-60 years, 60-70 years and 70-80 years), and -if applicable- treatment status. Diagnosis of metabolic syndrome was established if a subject satisfied at least three out of five criteria according to the modified guidelines of the National Cholesterol Education Programs Adults Treatment Panel III (NCEP ATPIII criteria): (1) systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg and/or use of antihypertensive medication; (2) HDL cholesterol levels < 1.03 mmol/l in men and < 1.30 mmol/l in women and/or use of lipid-lowering medication influencing HDL levels; (3) triglyceride levels ≥ 1.70 mmol/l and/or use of triglyceride-lowering medication; (4) waist circumference ≥ 102 cm in men and ≥ 88 cm in women; (5) fasting glucose level ≥ 5.6 and/or use of blood glucose-lowering medication and/or diagnosis of type 2 diabetes.[26] Coronary artery disease was defined when subjects reported any of the following diseases: myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting.

All analyses were conducted using PASW Statistics (Version 24, IBM, Armonk, NY, USA). Data are presented as mean ± SD, or median and interquartile range when not normally distributed. Means were compared between groups with analysis of variance. When variables were not normally distributed, medians were compared with the nonparametric Kruskal-Wallis test. Chi-square test was used to analyse categorical variables. To adjust for multiple comparisons, a p-value < 0.01 was considered statistically significant.

RESULTS

Participant characteristics are given in *table 1* and in the *Appendix, table 1*. In total, data of 87,648 individuals were available for analysis.

Clinical characteristics

Overall, women had a lower BP and generally more favourable lipid profiles, with lower LDL-C and triglyceride levels, and more women had a normal BMI than men. A similar percentage of men and women were treated with BP-lowering drugs, but fewer women used statins. In total, 10.8% of participants were using BP-lowering drugs, and 1.6% used more than two types of BP-lowering medication. In comparison with normal weight individuals, overweight and obese people had higher levels of BP, heart rate, glucose and lipid levels. More overweight and obese participants were treated with BP-lowering drugs and statins. For each BMI class, women had lower levels of BP, creatinine, LDL-C and triglycerides, and higher levels of HDL-C compared with men. Fewer women than men were current smokers, and used cholesterol-lowering drugs.

Effects of age and treatment on BP

In those not using BP-lowering drugs, the BP increased gradually in each age group, with mean levels of 126/69 mmHg in men and 117/68 mmHg in women aged 18-30 years, which gradually increased with higher age to levels of 139/78 mmHg in men and 138/73 in women aged 70-80 years (*Appendix, table 2*). In general, participants using BP-lowering drugs still had higher BP levels compared with individuals not using BP-lowering drugs, except in the male participants over the age of 60, and female participants aged 70-80 years. The largest difference in BP between treated and not-treated individuals amounted to 13/5 mmHg in the youngest males, and 13/10 mmHg in the youngest female group using two BP-lowering drugs (both p < 0.001). *Appendix, figure 1* depicts the percentage of individuals, stratified for age, who had elevated systolic BP ≥ 140 mmHg in each of the medication groups. Despite the use of BP-lowering medication(s), still a significant number of participants had insufficiently controlled BP: 30-50% of men and 20-50% of women do not achieve the desired target levels of systolic BP < 140 mmHg. In the participants not using BP-lowering drugs, especially in those over the age of 50 years, still 14-45% would be eligible for treatment based on a BP level ≥ 140 mmHg. The figure also shows that fewer women than men have elevated BP ≥ 140 mmHg.

BP: obesity vs. normal weight and overweight

Next, we analysed differences in BP according to the level of BMI (*figures 1A and 1B*). BP levels were significantly higher in all age groups in obese vs. normal weight and overweight individuals, in both men and women. This difference was the largest in the youngest age group (+11 mmHg in obese men, p < 0.001 vs. overweight and normal weight). In normal weight and overweight men and women, there was a clear difference in BP levels for all age groups (except the 70-80 year group) between untreated and treated individuals. This was less apparent in the obese. It should be noted that the use of BP-lowering medications was much higher in obese participants (*figure 2*). Despite this, a larger percentage of obese individuals had elevated systolic BP ≥ 140 mmHg (treated and untreated). Depending on the age group, 14%

Table 1. *Characteristics of the normal weight, overweight and obese study participants*

	Men			Women		
	Normal weight N = 13,762	Overweight N = 17,473	Obese N = 4,808	Normal weight N = 26,341	Overweight N = 17,194	Obese N = 8,070
Age (years)	42.0 ± 12.6	46.8 ± 11.6#	47.1 ± 10.7#	42.2 ± 11.9	46.6 ± 12.0#	46.0 ± 11.7
BMI (kg/m²)	23.0 ± 1.5	27.1 ± 1.4 #	32.7 ± 2.8 #	22.4 ± 1.6*	27.1 ± 1.4#	33.9 ± 3.8*#
Waist circumference (cm)	86 ± 6	97 ± 6#	111 ± 9#	79 ± 7*	90 ± 7 *#	104 ± 10*#
Smoking						
- Current smokers (%)	24.0	22.1#	23.3	20.9*	19.2*#	17.1*#
- Ex-smokers (%)	25.8	36.5#	38.2#	28.9*	36.1#	35.9#
Systolic BP (mmHg)	126 ± 13	132 ± 13#	137 ± 14#	118 ± 14*	124 ± 15*#	129 ± 15*#
Diastolic BP (mmHg)	74 ± 9	78 ± 9#	80 ± 9#	70 ± 8*	73 ± 9*#	74 ± 9*#
Heart rate (b/min)	69 ± 11	70 ± 11#	73 ± 11#	72 ± 10*	72 ± 10*	74 ± 11*#
Creatinine (µmol/l)	81 ± 12	83 ± 13#	83 ± 12#	67 ± 9*	67 ± 9*	66 ± 10*#
Glucose (mmol/l)	4.9 ± 0.4	5.1 ± 0.5#	5.3 ± 0.5#	4.7 ± 0.4*	4.9 ± 0.5*#	5.1 ± 0.5*#
Total cholesterol (mmol/l)	4.9 ± 1.0	5.2 ± 1.0#	5.3 ± 1.0#	4.9 ± 1.0	5.2 ± 1.0#	5.1 ± 1.0*#
HDL-cholesterol (mmol/l)	1.41 ± 0.32	1.26 ± 0.29#	1.14 ± 0.26#	1.70 ± 0.39*	1.56 ± 0.37*#	1.40 ± 0.33*#
LDL-cholesterol (mmol/l)	3.19 ± 0.87	3.51 ± 0.88#	3.52 ± 0.89#	2.93 ± 0.85*	3.26 ± 0.90*#	3.30 ± 0.87*#
Total/HDL-cholesterol ratio	3.65 ± 1.06	4.35 ± 1.27#	4.83 ± 1.34#	2.98 ± 0.82*	3.47 ± 0.99*#	3.83 ± 1.09*#
Triglycerides (mmol/l)	1.11 ± 0.66	1.51 ± 1.02#	1.82 ± 1.19#	0.88 ± 0.44*	1.09 ± 0.57*#	1.30 ± 0.76*#
% of participants with:						
- Metabolic syndrome	3.3	19.9#	57.7#	2.1*	14.2*#	35.6*#
- Coronary artery disease	1.1	2.9#	4.6#	0.3*	0.7*#	1.0*#
% of participants using:						
- BP-lowering drugs	5.1	12.3#	20.6#	6.3*	13.2#	21.4#
- Cholesterol-lowering drugs[a]	2.8	7.6#	10.5#	2.0*	4.5*#	5.4*#

Data are given as numbers or percentage, mean ± SD. BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Coronary artery disease = self-reported myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG).
[a]only statins *p < 0.001 vs men; #p < 0.001 vs. non-obese.

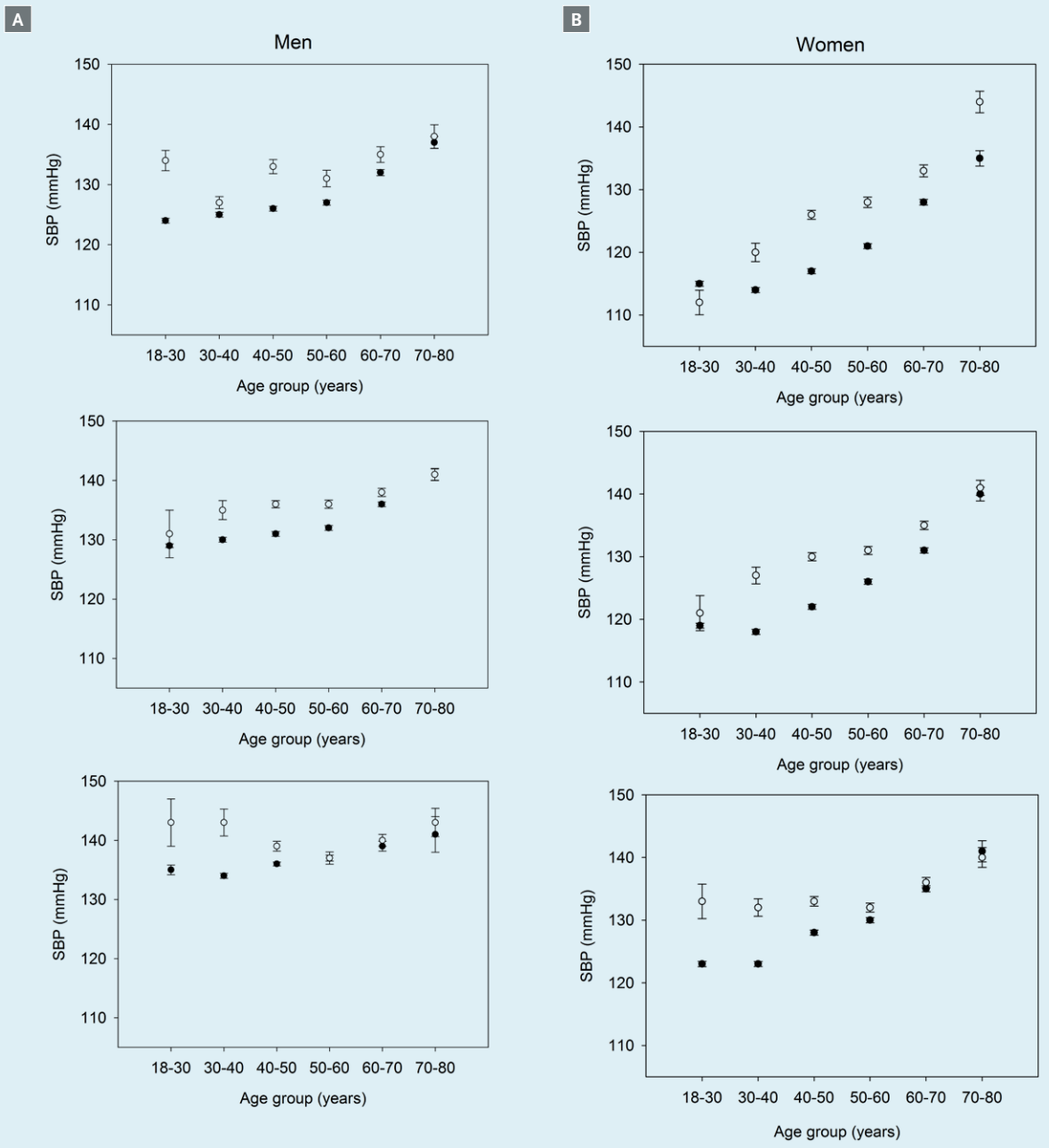
in the youngest and 52% in the oldest obese participants were not treated with BP-lowering medication, while for normal weight individuals this varied between 4% and 39% (*figure 2*). For obese participants treated with BP-lowering drugs, 35% in the lowest age group and 49% in the highest age group had systolic BP ≥ 140 mmHg. For normal weight participants these percentages were 15% and 50%, respectively.

LDL-cholesterol: obesity vs. normal weight

Overall mean LDL-C was 3.52 ± 0.89 mmol/l in obese vs. 3.19 ± 0.87 mmol/l in normal weight men (p < 0.001), and 3.30 ± 0.87 vs. 2.93 ± 0.85 mmol/l in normal weight women (p < 0.001). Overweight participants had an LDL-C similar to those who were obese. In men, overall 6.2% were using statins, which was 0.3% in the youngest age group and 27% in the oldest age group. In addition, 10.5% of obese men vs. 2.8% of normal weight and 7.6% of overweight men were using a statin (p < 0.001). In women, overall statin use was 3.3%, with 0.2% in the youngest age group and 20% in the oldest age group, respectively. More obese women were using statins than those with normal weight (5.4% vs. 2.0%, p < 0.001).

Figure 3 shows that LDL-C levels increased with age in both sexes, with higher levels in obese vs. normal weight individuals at all ages, while it remained at a constant level

Figure 1. *Levels of systolic blood pressure (± SEM) in normal weight (top panels), overweight (middle panels) and obese (bottom panels) individuals according to age group, sex (part A: men; part B: women), and treatment with BP-lowering drugs. Closed circles = no BP-lowering drugs; open circles = users of BP-lowering drugs*

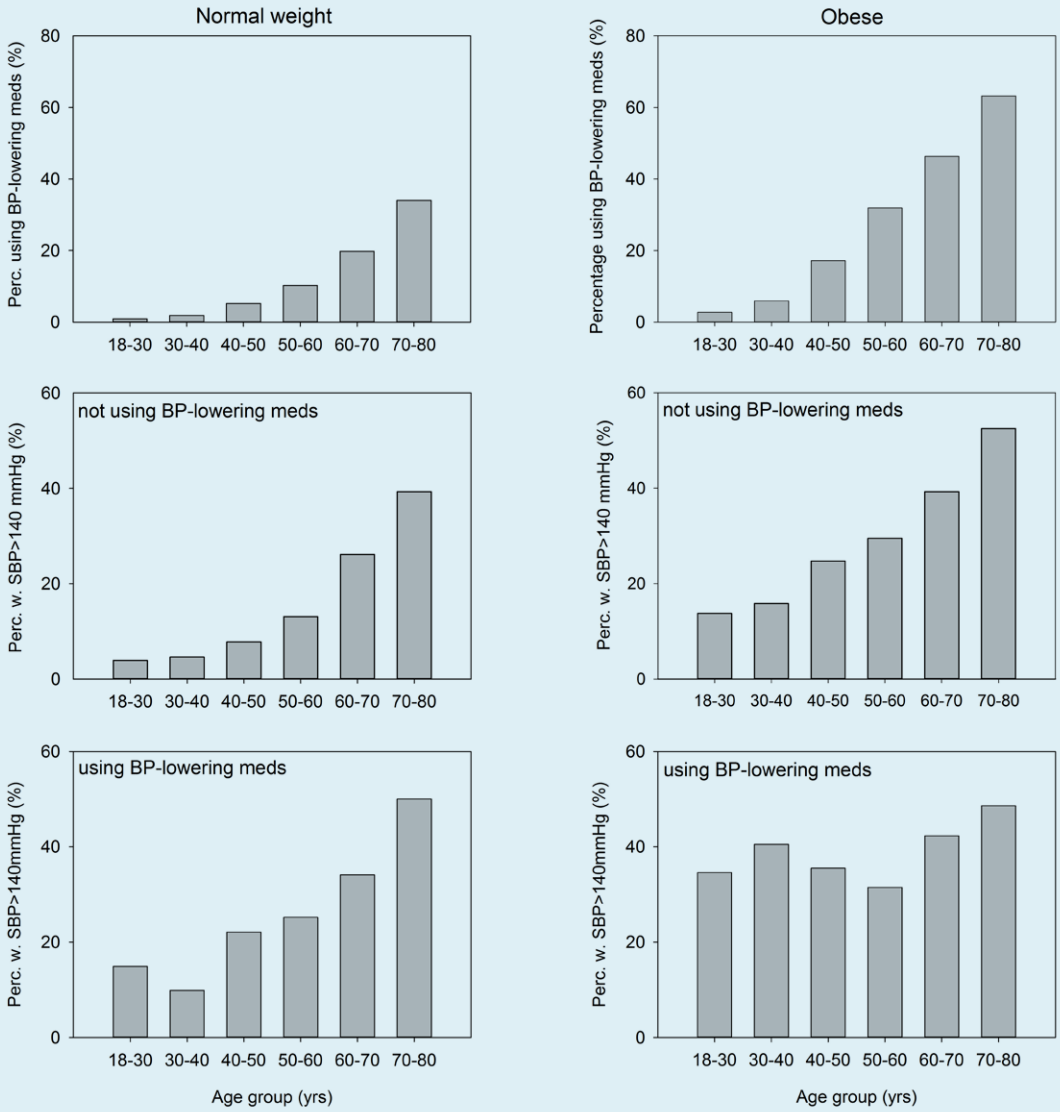


in those using statins. As can be seen, mean LDL-C levels varied between 2.5 and 3.0 mmol/l in men and women using statins. The overall number of statin users reaching an LDL-C target < 2.5 mmol/l was 37% in men and 29% in women. More untreated obese than normal weight participants had an LDL-C ≥ 3.5 mmol/l (men: 56% vs 37%, women: 41% vs 24%, both $p < 0.001$).

Combined risk factor treatment

Finally, we assessed lipid treatment and its levels in relationship to BP medication (combined risk factor intervention). There were slight differences of combined BP-lowering and statin treatment according to BMI. In normal weight, overweight and obese men treated with BP-lowering medication, 26%, 33% and 33% were

Figure 2. *Percentage of participants using BP-lowering medication, and of obese vs. normal-weight participants (both sexes) with systolic BP ≥ 140 mmHg in those not treated and treated. Left panels: normal weight (BMI 18-25 kg/m²). Right panels: obese (BMI > 30 kg/m²)*



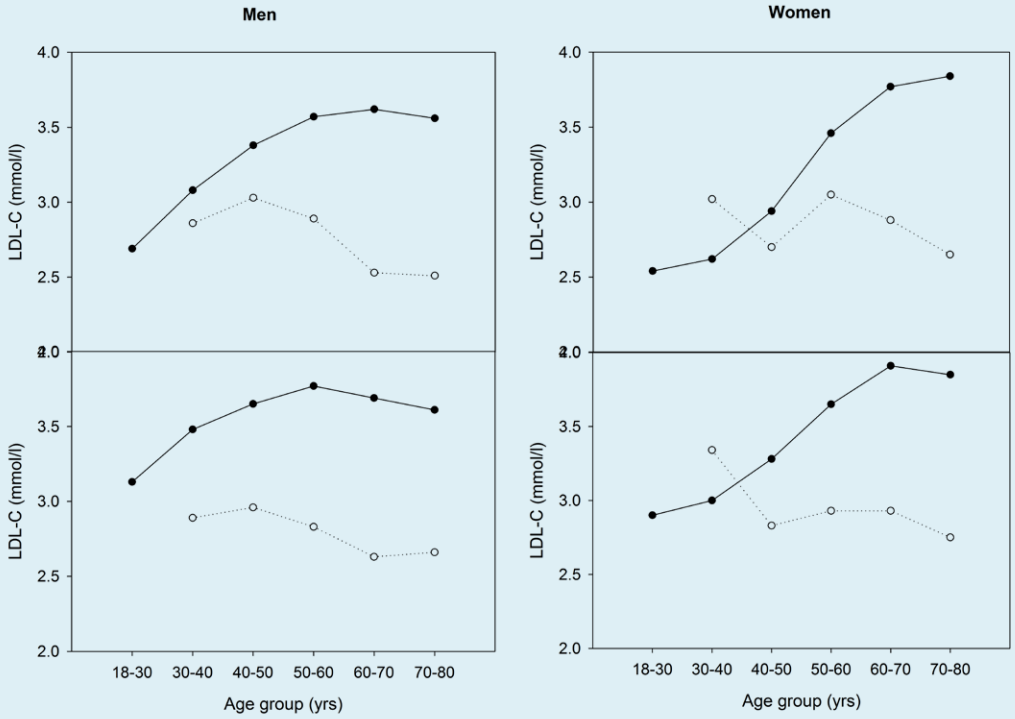
also using statins; in women, these percentages were significantly lower, i.e. 15%, 20% and 16%, respectively.

DISCUSSION

We found that in people of Western-European descent, obese individuals of both sexes have a higher BP and LDL-C compared with overweight and normal weight individuals, and especially obese men younger than 50 years have elevated BP levels. Use of BP-lowering drugs does not revert BP back to levels normal for the specific age group, and 10-50% of individuals in the various age groups do not achieve the desired target levels of systolic BP < 140 mmHg. Although cholesterol-lowering statins abolish the age-related increase in LDL-cholesterol in both men and women, the majority do not reach the target level of < 2.5 mmol/l.

The changes of BP levels with ageing were compared between individuals not using BP-lowering medications, and those who were treated with these drugs. Due to the large number of participants, we were able to stratify not only for sex, age and BMI, but also for the number of different BP-lowering medications used. We clearly demonstrated an age-dependent increase of BP, and significantly higher BP levels in men compared with

Figure 3. *Mean levels of LDL-cholesterol (mmol/l) in male and female participants according to age group and statin treatment. Upper panels: normal weight. Lower panels: obese individuals. Closed circles and solid line = no statins; open circles and dotted line = users of statins. Data at the bottom of each plot revert to the percentage of each age group using a statin*



women. In the participants not using BP-lowering drugs, especially in those over the age of 50 years, still up to 45% would be eligible for treatment based on a BP level ≥ 140 mmHg. In addition, despite treatment with one or more BP-lowering drugs, 30-50% of men and 20-50% of women do not achieve the desired target levels of systolic BP < 140 mmHg. This has also been reported in earlier cohort studies, for instance the German population-based cohort SHIP,[27] the Hispanic Community Health Study[28] and a study in rural Australia,[29] which clearly showed that the proportion of participants receiving therapy and the number of participants reaching their target BP values were insufficient. Similar observations have been reported in diabetic individuals.[30,31] Very recent data from the EPIC prospective cohort study confirmed that, amongst others, overweight, obesity, and hypertension contributed significantly to premature death.[32]

We used a cut-off level of 140 mmHg, as current guidelines advise to start treatment at a systolic BP ≥ 140 mmHg, and to lower until systolic BP levels < 140 mmHg have been reached.[5] The use of this BP goal is likely to explain why many participants do not reach BP levels which are 'physiological' for their age. This difference between 'normalisation' of BP vs. 'achieving treatment targets' may be of clinical relevance, as there may be additional cardiovascular benefit from more aggressive BP-lowering treatment. There are several studies which support this concept, as summarised by Ettehad et al.,[33] who suggested that lowering BP to systolic levels < 130 mmHg may be feasible and beneficial. As an example, the Hypertension Optimal Treatment (HOT) study showed that the optimal target for cardiovascular protection was in the range 80-85 mmHg for diastolic BP and in the range 130-140 mmHg for systolic BP, and especially people with diabetes seemed to benefit from further BP reduction.[34] However, there are indications that in some groups of patients, especially elderly people, this risk of aggressive BP-lowering may offset the benefits due to the so-called J-curve.[35]

We found a clear BP difference between men and women. Despite this, we observed that a similar percentage of both sexes were treated with BP-lowering medication. As we do not have any data regarding pre-treatment BP levels we can only speculate on the causes of these differences. It is apparent that fewer men reach treatment targets than women. This may be associated with a higher health consciousness in women, and the finding that women are more likely to visit their general practitioner than men.[36] Of course, the BP values in the participants not using any medication depend on how often and rigorous GPs have

been assessing them for high BP. In a situation where cardiovascular risk management is implemented fully, more people are screened, and therefore treated, for high BP.

Interestingly we found that the age-related increase in LDL-C was abolished by statin therapy and that contrary to BP-lowering medication, LDL-C levels are consistently lower in participants using statin treatment than those not using this medication. Mean LDL-C level on statin treatment varied between 2.5 and 3.0 mmol/l, indicating that a large number of participants did not reach the desired LDL-C level of < 2.5 mmol/l. Therefore, also these individuals can benefit from treatment intensification, for instance by switching from simvastatin to a more potent statin. However, we have to realise that LDL-C targets depend on integrated risk estimations,[4-8] for which we do not have sufficient data in the individual participant.

At all ages, obese participants had higher levels of BP and LDL-C in comparison with overweight and normal weight participants. This is of clinical relevance, as people with a BMI above 30 kg/m^2 clearly exhibit an increase in cardiovascular morbidity and mortality. Dudina et al. showed that obesity relates to CVD mortality in a strong and graded manner, especially in women and in younger persons.[37] Earlier studies have also reported that BP increases with increasing waist-to-hip ratio.[38] Obesity is a major contributor to chronic CVD and diabetes, and is also considered a key risk factor for hypertension. This applies to different countries, as a recent collaborative paper showed that elevated – and often untreated – BP ≥ 140 mmHg was present in 45-70% of obese individuals in an international study including cohorts from Germany, United Kingdom, Norway, Finland, Italy, Estonia and the Netherlands.[15] Data from the NHANES study support this, and Saydah et al. reported that the prevalence of hypertension and dyslipidaemia was 35.7 and 49.7%, respectively, in obese participants.[16] Although the same paper suggested that untreated hypertension and dyslipidaemia had decreased among obese adults,[16] recent observations have indicated a degree of clinical inertia in treating high BP, especially in obesity.[21,22] These recent papers are in contrast with a Dutch paper, which reported that obese men and women were more likely to consult their GP than persons without overweight, and more likely to receive drugs for the cardiovascular system.[39] On the other hand, studies in the UK and in Finland reported that delays in initiation or intensification of BP-lowering therapy, or insufficient BP control per se, were associated with increased risk of an acute cardiovascular event or death.[40,41]

This study can perhaps also be considered a large-scale benchmarking of cardiovascular risk management in our country. An earlier paper by Klijs et al. already showed that, adjusted for differences in demographic composition, the Lifelines adult study population is broadly representative for the adult population of the north of the Netherlands.[42] An important factor to consider in our results is the change of BP guidelines during the last decades. Treatment guidelines in 2003 and 2007 recommended a reduction of BP levels < 140/90 mmHg for uncomplicated hypertension and to < 130/80 for hypertension complicated by CVD, diabetes, or chronic kidney disease. In 2014 the JNC8 guidelines recommended less strict BP control, as a consequence of studies not showing any benefit of more aggressive BP control. In these guidelines, a cut-off of 150/90 mmHg for those over the age of 60 was proposed. The recent SPRINT study added new fuel to the debate, and suggested that a systolic BP in the 125-135 mmHg range is probably the optimal target for most hypertensive patients.[11] SPRINT was the first study to show a benefit for further reduction of BP levels in people over the age of 75 years.[43] However, it has been suggested that the unattended BP measurements performed in this study may corroborate with a 10 mmHg higher level in other studies.[44]

Strengths and limitations

Our study has some strengths and weaknesses. We have presented data for a large population-based study, in which all participants underwent careful examination, including structured and standardised BP measurements, and fasting LDL-C measurement in the same laboratory. Due to the large number of participants, we were able to stratify not only for sex, BMI and age group, but also for the number of different BP-lowering medications which were used by a participant. There are also a number of limitations. Measurements were performed at only one occasion, and physical examination was performed between 10 am and 6 pm. As a consequence, we could not control for possible diurnal variation of BP. Also, because of the cross-sectional nature, we only have information on current medication, and have no information on the response that a participant had exhibited earlier on the prescribed BP-lowering medication. Also, we did not have sufficient information to take statin dose into account.

Future directions

Large population-based studies such as Lifelines provide a lot of information on participants' habits, medical treatment and comorbidities on one hand, and the results of cardiovascular risk management in general practice on the other hand.[42] Studies such as this one would, however, immensely benefit from additional data obtained from the participants' general practitioners, provided cardiovascular risk management and responses to earlier medical and nutritional interventions are carefully recorded and can easily be obtained for research purposes. In Lifelines, participants provided informed consent to obtain these data, but accessing them still poses major logistic and

IT problems. Subsequent studies within Lifelines in which individual participants are interviewed about risk management and interventions may shed light on why people 'escape' cardiovascular screening programs. This also applies to better assessment of participants' lifestyle and nutritional habits, for instance alcohol and salt consumption, both important factors in BP control. Adding this information may improve current screening practices and perhaps help more people to obtain treatment goals.

With regards to the differences between obese and normal weight and overweight individuals, more attention should be directed to active screening of obese individuals, and – as mentioned before – reducing clinical inertia in treating high BP, especially in obesity.[21,22] A recent Dutch study on prescribing quality indicators reported that there is clear room for improvement in initiation and intensification of treatment of elevated glucose, lipids and BP for people with type 2 diabetes in primary care.[45] This strongly agrees with the findings on BP in the current study. Future studies should evaluate new strategies for earlier recognition of treatable cardiovascular risk factors, especially in obese people, and ways to improve active invitation of obese individuals in screening and lifestyle intervention and – if deemed necessary – medical intervention to reduce the burden of obesity. We have observed a similar need for a more active approach regarding post-partum follow-up and lifestyle intervention in women with pregnancy-induced diabetes.[46] Crucial for this are raised awareness and a more active approach towards screening.[47-50] Benchmarking of individual practices may help in recognising high-risk individuals and those in need for treatment intensification.[51,52] Studies on the long-term effect of specific interventions such as those in Sweden, in which primary care physicians are supported with lectures on BP treatment, a computerised decision support system with treatment recommendations, and yearly feedback on hypertension control, are ongoing.[53] Other approaches involve the specific role of the general practice nurse to identify, recall and manage patients with uncontrolled hypertension.[54]

CONCLUSION

In summary, obese individuals of both sexes have a higher BP and LDL-C compared with overweight and normal weight individuals, and especially obese men younger than 50 years have elevated BP levels. Use of BP-lowering drugs did not revert BP back to levels normal for the specific age group, whereas cholesterol-lowering statins abolished the age-related increase in LDL-C. These data suggest that more attention is needed for active screening and treatment of cardiovascular risk factors.

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DISCLOSURES

The authors state that there are no conflicts of interest.

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APPENDIX

Table 1. *Characteristics of the study participants*

	Men **N = 36,043**	**Women** **N = 51,605**
Age (years)	45.0 ± 12.1	44.3 ± 12.1#
BMI (kg/m²)	26.3 ± 3.6	25.8 ± 4.6#
BMI class 1, 2, 3 (%)	38.2 / 48.5 / 13.3	51.0 / 33.3 / 15.6#
Waist circumference (cm)	95 ± 10	87 ± 12
Current / ex-smokers (%)	23.0 / 32.6	19.7 / 32.4#
Systolic BP (mmHg)	130 ± 14	122 ± 15#
Diastolic BP (mmHg)	77 ± 9	72 ± 9#
Heart rate (beats/min)	70 ± 11	72 ± 10#
Creatinine (µmol/l)	82 ± 12	67 ± 9#
Glucose (mmol/l)	5.1 ± 0.5	4.8 ± 0.5#
Total cholesterol (mmol/l)	5.1 ± 1.0	5.0 ± 1.0#
HDL-cholesterol (mmol/l)	1.30 ± 0.31	1.61 ± 0.39#
LDL-cholesterol (mmol/l)	3.39 ± 0.89	3.10 ± 0.89#
Total/HDL-cholesterol ratio	4.15 ± 1.27	3.28 ± 0.98#
Triglycerides (mmol/l)	1.40 ± 0.96	1.01 ± 0.57#
% of participants with:		
- Metabolic syndrome	18.6	11.4#
- Coronary artery disease	2.5	0.5#
% of participants using:		
- BP-lowering drugs	10.7	11.0
- Cholesterol-lowering drugs[a]	6.2	3.3#

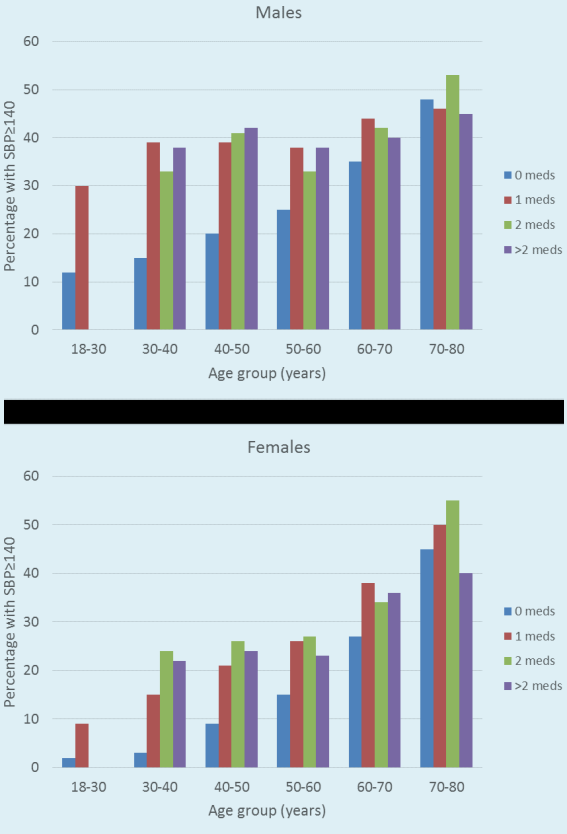
Data are given as numbers or percentage, mean ± SD, or median (IQR, interquartile range) when not normally distributed. BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
BMI class = 1: normal weight; 2: overweight; 3: obesity; [a]only statins; #$p < 0.001$.

Table 2. *Average systolic and diastolic blood pressure levels (mmHg) according to age, sex and treatment with BP-lowering medication*

Men	**Use of BP-lowering medication****			
Age group (years)	**0**	**1**	**2**	**> 2**
18-30	126/69	132/75$^{\$}$	139/74$^{\$}$	N.A.
N	(4136)	(29)	(8)	(2)
30-40	128/74	136/80$^{\#}$	135/76$^{\#}$	135/78$^{\$}$
N	(7719)	(138)	(52)	(16)
40-50	130/78	137/83$^{\#}$	136/82$^{\#}$	138/82$^{\#}$
N	(12068)	(644)	(281)	(116)
50-60	131/79	136/83$^{\#}$	134/81$^{\#}$	135/80$^{\&}$
N	(5163)	(583)	(261)	(110)
60-70	135/79	139/80$^{\#}$	137/80$^{\$}$	137/78
N	(2594)	(627)	(385)	(144)
70-80	139/78	140/78	142/78	139/75
N	(514)	(247)	(128)	(67)
Women	**Use of BP-lowering medication****			
Age group (years)	0	1	2	> 2
60-70	117/68	118/69	129/78&	N.A.
N	(6891)	(81)	(5)	(2)
70-80	117/70	125/76$^{\#}$	130/78$^{\#}$	133/79$^{\#}$
N	(10656)	(277)	(63)	(18)
60-70	120/72	129/77$^{\#}$	131/78$^{\#}$	130/79$^{\#}$
N	(17127)	(1130)	(426)	(132)
70-80	124/73	130/76$^{\#}$	131/76$^{\#}$	131/77$^{\#}$
N	(7381)	(985)	(446)	(121)
60-70	131/73	135/75$^{\#}$	134/74$^{\#}$	135/73$^{\$}$
N	(3282)	(813)	(478)	(156)
70-80	138/73	142/75$^{\$}$	141/74	139/71
N	(592)	(258)	(178)	(83)

N.A. not ascertained because of n < 5 in this group; **number of different classes of BP-lowering medications; $^{\#}p < 0.001$, $^{\$}p < 0.005$, $^{\&}p < 0.01$ vs no treatment.

Figure 1. *Percentage of patients with elevated systolic blood pressure (SBP ≥ 140 mmHg) according to number of BP-lowering agents used (0, 1, 2, > 2). Top panel: men; bottom panel: women*



CASE REPORT

Nephrotic syndrome due to lupus-like glomerulonephritis in an HIV-positive patient

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ABSTRACT

Lupus nephritis, a well-known complication in systemic lupus erythematosus, is characterised by a proliferative glomerulonephritis or membranous nephropathy along with a full-house immunofluorescence pattern on renal biopsy. There are very few exceptions in which similar histopathological findings are present, but case reports show that an increasing number of HIV-positive patients (mostly black Africans, but also white patients) have HIV-immune complex disease (HIVICK), which can mimic lupus nephritis. Lupus-like HIVICK is treated differently than 'true' lupus nephritis, so distinction is warranted.

KEYWORDS

HIV immune complex kidney disease, HIV-associated nephropathy, HIVAN, HIVICK, lupus-like glomerulonephritis

What was known on this topic?

HIV infection is associated with various nephropathies, with HIV-associated nephropathy (HIVAN) being the most common. After introduction of combination antiretroviral therapy, the epidemiological spectrum of HIV-associated renal pathology has changed with a relative decrease of HIVAN and an increase of drug-induced tubular disease, HIV-immune complex kidney disease and HIV-associated comorbidities such as hepatitis C, diabetes mellitus and hypertension.

What does the case add?

Although nephrotic syndrome is a well-known manifestation in HIV-positive patients, it is mostly associated with HIVAN. Nephrotic syndrome due to lupus-like glomerulonephritis is far less common. Furthermore, this is the first case where lupus-like glomerulonephritis was the presenting manifestation of HIV infection. This case report also shows that antiretroviral treatment, together with antiproteinuric medication, may have a marked favourable effect on proteinuria and renal function.

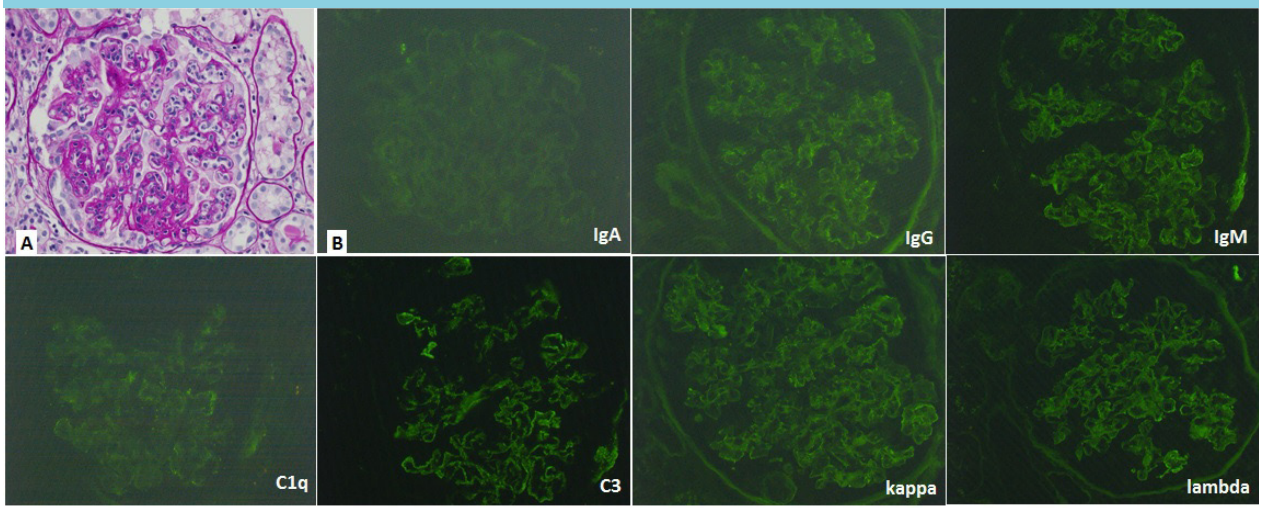
CASE REPORT

A 26-year-old Caucasian female was referred to our centre for a second opinion. A few weeks earlier, she was admitted to another hospital with malaise, generalised weakness and peripheral oedema of the lower extremities. Medical history included perinatal asphyxia and pulmonary embolism without an apparent cause (at the age of 24 years).

On physical examination, she was hypertensive (blood pressure 150/114 mmHg) and had severe oedema in both legs. Physical examination was otherwise unremarkable. Serum creatinine was elevated (*table 1*) and urinalysis showed glomerular erythrocyturia with 30-50 erythrocytes per high power field with < 1% acanthocytes and a few erythrocyte casts. Proteinuria was 13.1 g/24 hours. The differential diagnosis consisted of membranous nephropathy (including lupus), membranoproliferative glomerulonephritis or IgA nephropathy. A kidney biopsy showed active, diffuse and global lupus nephritis class 4/5 with endocapillary and mesangial proliferation and few sclerotic lesions. Immunofluorescence staining was positive for IgA, IgG, IgM, light chain type lambda and kappa and C1q/C3 (*figure 1*), Congo red was negative. Electron microscopy was not performed. Additional screening for ANA, ENA, and anti-DNA was negative; a weak cryoglobulin type 3 was detected along with a low complement factor C3 (0.69 g/l; normal 0.90-1.8 g/l) and normal C4 (0.21 g/l; normal 0.10-0.40 g/l).

Except for a dubious facial rash and pancytopenia (without haemolysis) there were no other criteria for systemic lupus

Figure 1. *a) PAS staining of a representative glomerulus. Endocapillary proliferation consists of the presence of neutrophils and lymphocytes and endothelial cell enlargement. There is mesangial proliferation and a small sclerotic lesion. b) Immunofluorescence studies demonstrate mesangial and membranous staining in the characteristic 'full house' pattern, i.e. positive staining for all immune reactants (IgA, IgG, IgM, C1q, C3, kappa and lambda light chains)*



erythematosus. The negative ANA and anti-DNA was also inconsistent with lupus disease, so another underlying disease was sought. Additional investigation revealed an HIV-1 infection with a viral load of $1.52*10^6$ copies/ml and CD4 count $0.13*10^9$/l (reference range $0.4\text{-}1.3*10^9$/l). Serology for hepatitis B and C was negative. Antiviral therapy was started (dolutegravir, abacavir and lamivudine) in combination with antiproteinuric drugs (furosemide and enalapril). Along with a favourable virological response, renal function improved and the nephrotic syndrome went into partial remission (*table 1*).

DISCUSSION

The most common HIV-associated nephropathy is focal segmental glomerulosclerosis (known as HIV-associated nephropathy, HIVAN), which was first reported in the USA in 1984. It is characterised by nephrotic range proteinuria, renal dysfunction and collapsing focal segmental glomerulosclerosis, due to direct viral infection of renal cells or the action of viral proteins.[1] Without combination antiretroviral therapy (cART) renal function often rapidly progresses to end-stage renal disease. Treatment with cART is therefore considered mandatory.[2] Due to the introduction of antiretroviral treatment, the incidence of HIVAN has decreased. This has changed the epidemiological spectrum of renal pathology associated with HIV, with a relative increase in other nephropathies such as HIV-immune complex kidney disease, cART-induced tubulotoxicity and HIV-associated comorbidities such as hepatitis C virus infection, diabetic nephropathy and nephrosclerosis.[1,3-5] Thrombotic microangiopathy and amyloid A amyloidosis are less frequently seen, but are also associated with HIV and kidney disease.

HIVICK is characterised by the presence of glomerular and mesangial immune deposits and consists of a broad spectrum of histopathological entities such as membranous nephropathy and lupus-like nephritis.[5] According to the literature, patients with HIVICK generally have less advanced HIV infection, usually have only mild proteinuria and less frequently progress to end-stage renal disease compared with HIVAN.[5,6] In retrospective case series of HIV-positive patients, HIVICK is found in about 4-30% in renal biopsies (mostly reported as membranous nephropathy, and only rare cases described as lupus-like nephritis).[1,4,6] However, selection bias may have underestimated the true incidence of HIVICK. The pathogenesis of HIV infection in immune complex renal disease is poorly understood, and treatment is also less obvious. Most patients with immune complex kidney disease are already treated with cART, but for those who have not yet received antiretroviral therapy, such as this patient, treatment may have beneficial effects on renal outcome.[1,5-10] Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are often prescribed in order to control blood pressure and proteinuria, with a few case reports that report prescribing immunosuppressive therapy.[5,10-12] More literature on pathogenesis, treatment and outcome is warranted in this upcoming renal disease.

Table 1. *Laboratory results*

	At presentation	After 1 year	Normal range
Serum			
Haemoglobin (mmol/l)	6.0	9.2	7.5-9.9
Leucocytes (10^9/l)	3.3	10.3	4.0-11.0
Lymphocytes (10^9/l)	0.99	NA	0.8-3.2
Thrombocytes (10^9/l)	110	348	150-350
Haptoglobin (g/l)	1.4		0.3-2.0
CRP (mg/l)	16	NA	< 10
Albumin (g/l)	13	43	35-50
Creatinine (µmol/l)	152	90	60-110
eGFR (ml/min/1.73 m^2)	40	76	> 90
ANA	Neg	NA	
AntiDNA (IU/ml)	1	NA	0-15
ANCA	Neg	NA	
Cryoglobulin	Weak*	NA	
Complement C3 (g/l)	0.69	NA	0.75-1.40
Complement C4 (g/l)	0.21	NA	0.10-0.34
Urine			
Protein (g/24h)	13.1	0.9	
Creatine clearance (mL/min)	40	118	
Selectivity index	37%	NA	

CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; ANA = antinuclear antibodies; AntiDNA = anti double stranded DNA; ANCA = Anti-neutrophil cytoplasmic antibodies; NA = not applicable. *a weak mixed cryoglobulin was detected (type III; polyclonal IgG).

DISCLOSURES

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

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CASE REPORT

Donor-derived tuberculosis via orthotopic liver transplantation

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ABSTRACT

We present a case of donor-derived tuberculosis after liver transplantation, in which the donor origin of the *Mycobacterium tuberculosis* isolate was made most likely by DNA fingerprinting. Screening for latent tuberculosis of transplant donors originating from high endemic areas with an ex-vivo interferon-gamma release assay should be considered.

KEYWORDS

Mycobacterium tuberculosis, donor-derived, liver transplantation

INTRODUCTION

Donor-derived infections remain a challenge after solid organ transplantation because screening of post-mortal donors is not possible for all potential pathogens. Whereas transmission of pathogens such as cytomegalovirus and Epstein-Barr virus is a known and accepted risk, other infections may be transmitted unexpectedly. Although the incidence of donor-derived infections is low at approximately 0.2%, recipient mortality may be as high as 25%.[1,2] We present a case of donor-derived tuberculosis after liver transplantation, in which the donor origin of the *Mycobacterium tuberculosis* isolate could be demonstrated by DNA fingerprinting.

CASE REPORT

A 70-year-old man, born in Suriname, was referred to our centre with rapidly progressive liver failure. His medical history consisted of recent cholecystitis, treated conservatively with amoxicillin-clavulanic acid. On admission, the Model for End-Stage Liver Disease (MELD) score was 23. Further workup excluded infectious, hereditary, vascular and autoimmune disorders. During pre-transplant screening, a tuberculin skin test and interferon gamma release assay (Quantiferon-TB Gold in-tube®) were both negative and chest radiography showed no abnormalities.

Due to progressive liver failure, the patient underwent orthotopic liver transplantation in November 2013. The donor was a 57-year-old woman from the Philippines who suffered from a lethal brain injury after a complicated resection of a pituitary adenoma. Histopathology of the recipient's explanted liver showed nodular regenerative hyperplasia and bland cholestasis, suggesting drug-induced liver injury as the cause of liver failure. Maintenance immunosuppression consisted of prednisolone and tacrolimus.

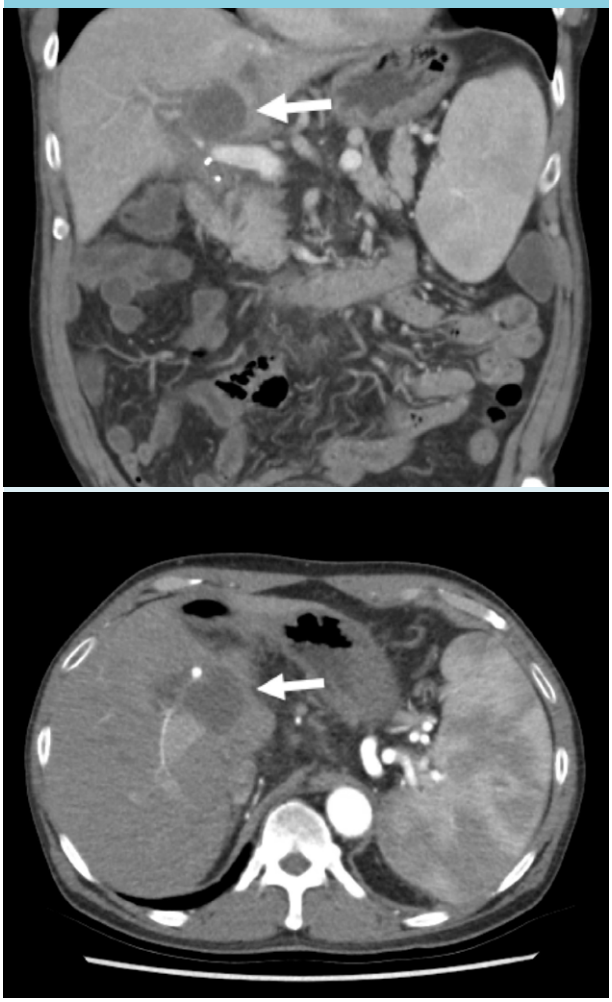
Six months post-transplantation the patient developed fever without other symptoms. A CT scan showed a mass of 3.3 × 3.7 cm in the liver hilum with portal vein thrombosis due to compression (*figure 1*). A diagnostic aspiration yielded pus. The Gram stain showed 5-20 leukocytes and 0-5 Gram-positive rods per high power field. Additional Ziehl-Neelsen staining showed +4 acid fast bacilli and a PCR for *M. tuberculosis* (MTB) complex (in-house, IS6110 target) was positive. Culture for common aerobic and anaerobic bacteria remained negative.

Since 1993, in the Netherlands all MTB isolates are routinely fingerprinted for epidemiological purposes at the Tuberculosis Reference Laboratory. Based on

spoligotyping, the MTB isolate found in the present case was characteristic of the Manilla genotype family, which is commonly found in immigrants originating from the Philippines.[3] Based on the genotype, characteristic of the donor's origin, it was concluded that the infection was probably donor-derived. During pre-transplant screening of the donor, abdominal ultrasound and chest radiography showed no abnormalities. No tests for latent tuberculosis had been performed. The infection was reported to Eurotransplant. To date, the recipients of the kidneys and pancreas of the same donor have not developed tuberculosis.

Treatment consisted of isoniazid, ethambutol, pyrazinamide and levofloxacin and a portal stent was placed. Rifampicin was not used because of the interaction with tacrolimus. The isolate was later found to be fully susceptible. Pyrazinamide was discontinued after five weeks because of rising uric acid levels and levofloxacin was discontinued after seven weeks because the patient wanted to resume running. It was planned to treat him for 18 months. However, after eight months of treatment the serum aminotransferases were elevated (SGOT 229 IU/l, SGPT 553 IU/l). The tuberculosis therapy was discontinued followed by normalisation of the liver enzymes. Because imaging showed complete resolution of the abscess, the treatment was not resumed and the patient remained well, the follow-up time being 29 months at the time of this writing.

Figure 1. *CT scan of the abdomen (upper panel coronal view; lower panel transverse view), arrows indicate the abscess located at the liver hilum*



DISCUSSION

Infections are among the most frequent complications after solid organ transplantation. They can be categorised as a manifestation of pre-existing chronic infection in the recipient, a reactivation of latent infection in the recipient, a donor-derived infection or as exogenous *de novo* infection. The percentage of infections that are donor-derived varies in different reports.[4,5]

The incidence of tuberculosis in solid organ transplant recipients is higher than in the general population.[6,7] The differentiation between endogenous reactivation and donor-derived infection can be difficult. A donor origin is very likely if infection is only localised in the transplanted organ or if multiple recipients from the same donor develop tuberculosis with an identical isolate.

Donor-derived tuberculosis from a liver transplant is rare, with only a few published cases.[8-10] In contrast to the lack of proof in those reports, the donor origin of the infection in our patient was deducted from the MTB fingerprint in combination with the donor origin from the Philippines, where that specific MTB genotype was known to circulate. While post-transplant tuberculosis is notorious for poor graft and patient survival, the early diagnosis with only localised disease probably contributed to a favourable outcome.[11]

Potential organ donors are thoroughly screened to reduce the risk of transmission of infections. Eurotransplant guidelines prescribe which information is required to minimalise this risk. Specific screening of living donors for latent tuberculosis is possible, although there is debate on the value of such screening and the need for treatment.[12] In case of post-mortal donors, screening for tuberculosis with skin testing is generally not feasible and the donor origin, a history of past tuberculosis or exposure and chest radiography have a very limited sensitivity for latent tuberculosis. Screening with a tuberculosis-specific interferon gamma release assay, which only requires a fresh blood sample, could be useful.[12]

The treatment of tuberculosis in transplant recipients can be challenging due to drug interactions and significant toxicity. According to current guidelines, treatment should be based on epidemiology and drug resistance.[13]

Treatment with a rifamycin is generally avoided because of interactions with calcineurin inhibitors and mTOR inhibitors. If a rifamycin is nevertheless used, the dose of immunosuppressive drugs has to be increased with close monitoring of drug levels. Significant hepatotoxicity can occur, especially when combining several hepatotoxic drugs including pyrazinamide, rifampicin and isoniazid.[14,15] Consultation with a tuberculosis expert is always indicated in case of post-transplantation tuberculosis.

CONCLUSION

This case with donor-derived tuberculosis after liver transplantation illustrates that donors originating from high tuberculosis endemic countries may transmit tuberculosis via a transplanted liver, although this is probably very rare. The early diagnosis probably contributed to the favourable outcome in our patient.

DISCLOSURES

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

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PHOTO QUIZ

Granulating wound after a holiday in Peru

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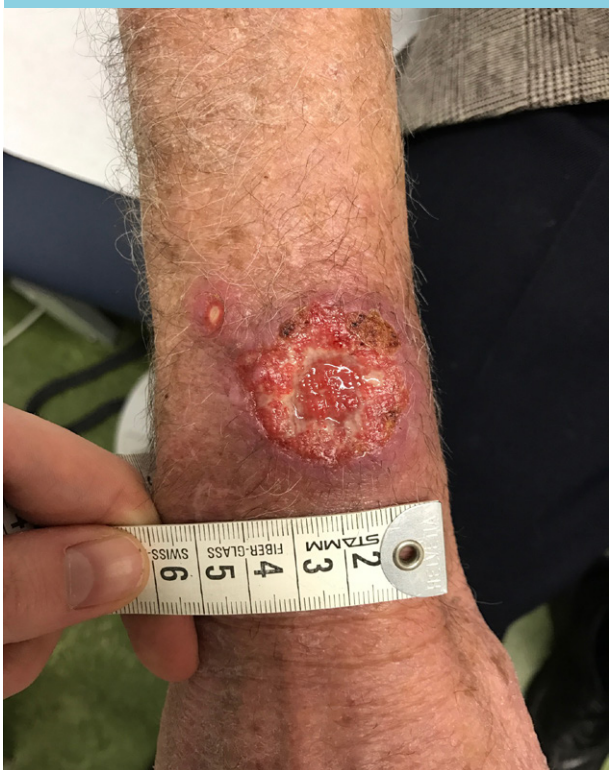
CASE REPORT

A 79-year-old man presented to our outpatient clinic because of a painful skin lesion on his right forearm. Four months after returning from a one-month trip in Peru he noticed a small crusted lesion on his forearm, which gradually increased into a painful ulcerative, granulating wound. On physical examination he did not appear ill. Body temperature was normal. A large, round, erythematous granulating ulcerative lesion of approximately 3 x 3 cm with raised edges was seen just proximal of his right wrist (*figure 1*). There was a nodular lymphangitis extending from the wound to the insertion of the deltoid muscle. Cubital and axillary lymphadenopathy were present. Laboratory analysis, including leucocyte count and C-reactive protein level, was unremarkable.

Figure 1. *Picture of the right forearm of the patient showing a typical volcano-shaped wet, ulcerating lesion with thickened edges of approximately 3 x 3 cm*



WHAT IS YOUR DIAGNOSIS?

See page 419 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 418)

GRANULATING WOUND AFTER A HOLIDAY IN PERU

DIAGNOSIS

Based on the typical ulcerating skin lesion with a background of his travel history, cutaneous leishmaniasis was suspected. A histological biopsy with a positive PCR for *Leishmania (Viannia) braziliensis* confirmed the diagnosis. The patient was treated with 6 doses of 3 mg/kg liposomal amphotericin B in a period of 4 weeks with a cumulative dose of 1400 mg, after which the skin lesions improved (*figure 2*).

Cutaneous leishmaniasis is an infection caused by various species of *Leishmania* protozoa and is endemic in more than 70 countries throughout Latin America, Asia, Middle-East and southern Europe. The global number of reported cases has increased in the past decades because of improved diagnosis and case notification, but also because of drug resistance and inadequate vector control as a result of urbanisation and deforestation.[1] *Leishmania* parasites are transmitted by sandflies belonging to either *Phlebotomus* spp (Asia, Europe, Middle-East and North-Africa) or *Lutzomya* spp (Central and South America). The ecological context of the transmission cycles between the Old World (i.e., Africa, Asia and Europe) and the New World (i.e., the Americas) is different. New World cutaneous leishmaniasis is mostly associated with forests, whereas an open semi-arid climate is the transmission environment for Old World cutaneous leishmaniasis. There are 17 different *Leishmania* species that can cause different clinical manifestations in humans. New World species of the *L. (Viannia)* subgenus, such as *L. (Viannia) braziliensis* and *L. (Viannia) peruviana* are associated with more severe and prolonged disease than the *L (Leishmania)* subgenus, such as *L. (Leishmania) mexicana* and *L. (Leishmania) amazonenis*.[2] After a bite of an infected sandfly, acute cutaneous leishmaniasis usually presents as a small erythema that develops into a papule and then a nodule. Over a period of 2 weeks to 6 months this nodule will enlarge and ulcerate to produce a typical volcano-shaped 'wet' lesion with thickened edges. Ulcerated lesions are typical of infection by New World species, whereas nodular lesions are caused by the Old World species *L. aethiopica* and *L. donovani*. Sporotrichoid lymphatic spread, regional lymphadenopathy and satellite lesions such as in our case are common. Although cutaneous leishmaniasis is generally non-fatal and self-limiting, the risk of developing mucosal leishmaniasis should be considered when deciding on local or systemic therapy. Mucosal leishmaniasis can be life-threatening and disfiguring when ulcerating and extensive tissue destruction of nasal cartilage, larynx, trachea or oesophagus can lead to death by aspiration, respiratory compromise or secondary respiratory infections. *L. braziliensis* is a species with a high risk for mucosal disease. For cutaneous leishmaniasis, parenterally or intralesionally pentavalent antimony (Pentostam) is the first treatment of choice.[3] However, because of the potential side effects of pancreatitis, cardiac toxicity and elevated liver enzymes, particularly in this older patient, we chose liposomal amphotericin B as second best alternative regimen.[3,4]

Figure 2. *Picture after treatment showing the reduced skin lesion with a crusted, necrotic centre with disappearance of the volcano-shape and thickened edges*

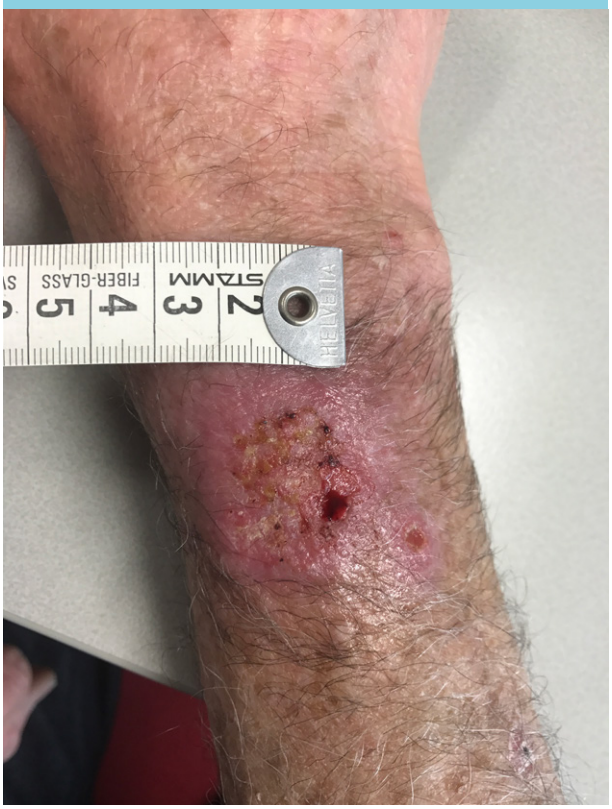


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PHOTO QUIZ

A rare cause of abdominal mass and deep venous thrombosis

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CASE REPORT

Our patient presented to the paediatric emergency department in 2006, when he was 14 years old, with a painful right lower abdominal mass; examination also revealed swelling of the right extremity. The ultrasound of the right extremity showed right femoral vein thrombosis extending up to the iliac vein. The patient underwent a computed tomography (CT) scan (*figure 1*) which suggested that instead of being a hernia, the mass was either caused by lymphadenopathy or dilated vessels. The patient underwent a magnetic resonance angiogram (MRA) (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 421 for the answer to this photo quiz.

Figure 2. *Magnetic resonance angiogram*

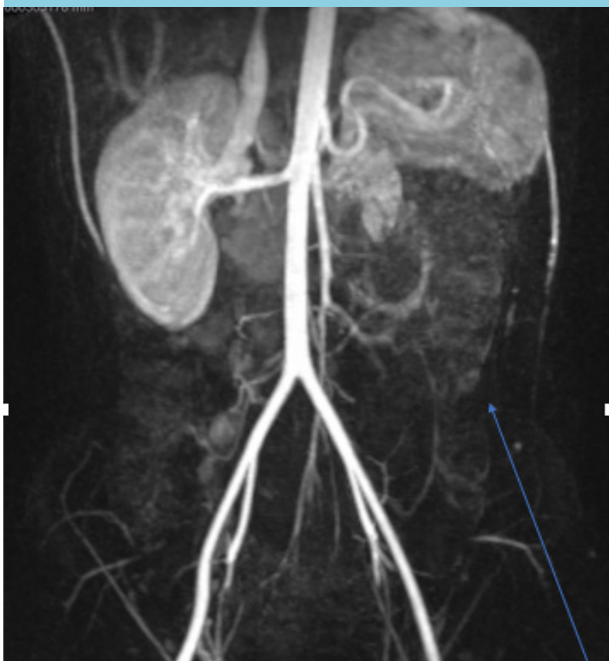
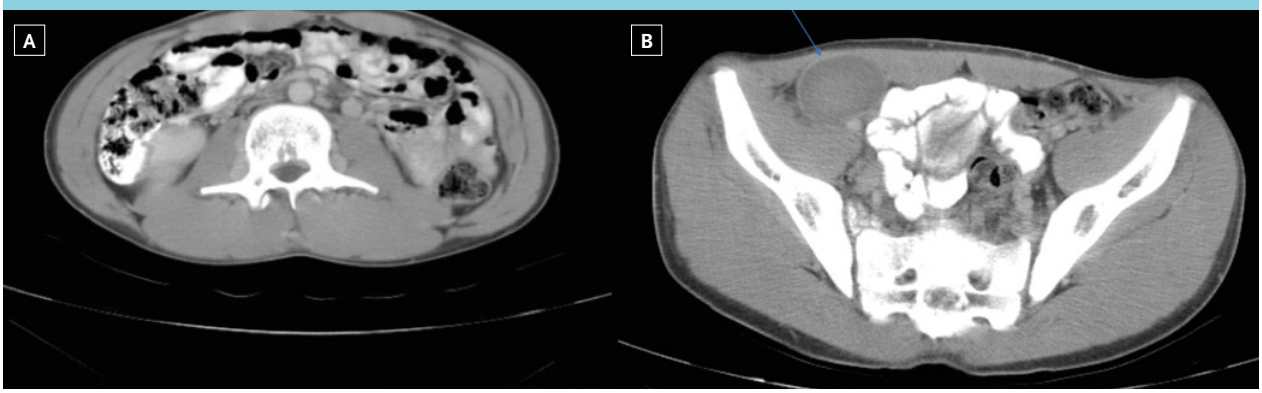


Figure 1. *A. CT scan suggesting either lymphadenopathy or dilated vessels. B. Collateral vessel (arrow)*



ANSWER TO PHOTO QUIZ (PAGE 420)

A RARE CAUSE OF ABDOMINAL MASS AND DEEP VENOUS THROMBOSIS

DIAGNOSIS

The computed tomography scan and MRA showed absence of inferior vena cava. Left renal hypoplasia was also noted and a renal perfusion study demonstrated decreased blood flow to this kidney. The right common iliac drained into the azygous vein and the left common iliac drained into hemizygous vein. The deep venous thrombosis (DVT) was initially treated with heparin and then bridged to warfarin, but he only attended follow-up in the clinic intermittently and had a poor medication compliance. After 4 years, a repeat ultrasound showed a subacute left femoral thrombus with persistence of the right iliac thrombus, so he was advised to continue warfarin therapy. Because follow-up and medication compliance proved challenging for this patient, he was offered treatment with a direct oral anticoagulant, rivaroxaban, when he was 25. For the past 3 years, he has been stable with no clinical evidence of a new DVT.

DISCUSSION

Inferior vena cava agenesis (IVCA) is a rare abnormality[1] that predisposes patients to DVT. In the absence of any associated symptoms or visceral defects, patients are generally undiagnosed unless the condition is discovered as an incidental finding. When symptomatic, patients typically present with lower extremity swelling and pain, and are subsequently diagnosed with unprovoked DVT.

The increased risk of DVT in patients with IVCA is most likely multifactorial. In these cases, the veins of the lower limbs drain into the azygous and hemizygous veins which have smaller lumens. Thus, there is congestion and stasis with consequently an increased risk of DVT. In addition to this anatomical predisposition, patients with IVCA may have an increased incidence of other prothrombotic conditions such as protein C deficiency, factor V Leiden mutation, and hyperhomocystenaemia.[2] The development of new thromboses, as in our patient, emphasises the importance of meticulous follow-up.

Renal aplasia is commonly reported in IVCA with right renal aplasia being more common as the right metanephros drains directly into the IVC[3] while the left metanephros drains into the left gonadal vein which drains into the lumbar perforators. There are some reports of left renal agenesis with IVCA[4] but these are uncommon and the cause is less clear.

Ultrasound is the preferred imaging modality to diagnose DVT but CT or MRI is ideal to identify IVC abnormalities. The dilated collaterals in these patients pose diagnostic challenges as, when in the abdomen or thorax, they can even mimic malignant masses.[2] Appropriate imaging of these patients is vital to formulate treatment plans.

There are no recommended guidelines for the treatment of IVCA and previously reported therapies have ranged from chronic anticoagulation to surgical reconstruction of the IVC. Anticoagulation with warfarin is the most commonly used treatment modality. Given the continued predisposition to thrombus, these patients require lifelong anticoagulation.[5]

In conclusion, a high index of suspicion for IVCA is advised especially for the younger patient who presents with an unprovoked DVT. Patients require lifelong anticoagulation due their predisposition to thrombosis, and as such, require close follow-up in the outpatient setting.

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PHOTO QUIZ

A blood smear on admission

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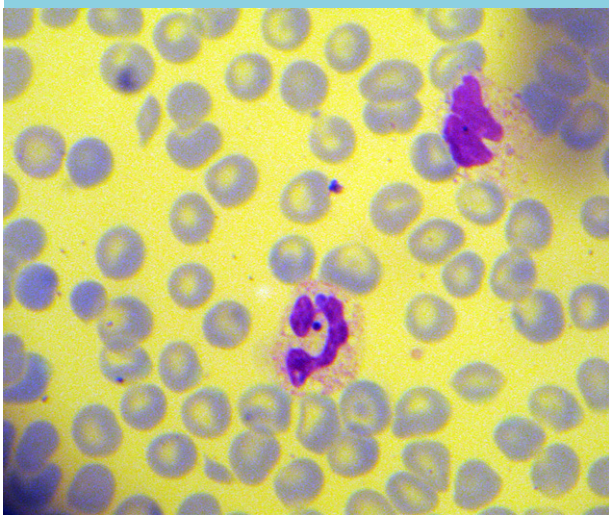
CASE REPORT

A 69-year-old woman was admitted to the intensive care unit (ICU) with a one-day history of coughing, nausea and drowsiness. She was a profound smoker and drank 3 units of alcohol daily. Medical history revealed myocardial infarction. Known prescribed medications were metoprolol, quinapril, pravastatin and carbasalate calcium. Physical examination showed a respiratory rate of 35/minute, heart rate of 82/minute, blood pressure of 129/62 mmHg and a tympanic temperature of 36.1°C. She had a poor circulation with cold extremities and prolonged capillary refill. We observed a Glasgow coma scale of E3M5V3, no meningism or skin abnormalities; lumbar puncture was not performed because of low suspicion and severe coagulopathy. She had poor dental condition and had recently lost a tooth. Blood gas analysis showed mild respiratory compensated metabolic acidosis (pH 7.47, pCO_2 3.6 kPa, HCO^{3-} 19.7 mmol/l, base excess -3.1 mmol/l) and reasonable oxygenation (pO_2 9.1 kPa, $SatO_2$ 95%). Laboratory results showed a normal haemoglobin level (8.7 mmol/l), leucocytopenia/thrombocytopenia (2.8 x 10^9/l and 50 x 10^9/l, respectively), severe coagulopathy (APTT 80 seconds, PT 31 seconds, INR 2.0), C-reactive protein 237 mmol/l, lactate 3.6 mmol/l, creatine kinase 1096 U/l and acute kidney injury with a creatinine of 150 µmol/l. Chest X-ray and CT scan of the cerebrum, thorax and abdomen showed no abnormalities. We suspected sepsis, collected blood cultures and started treatment with broad-spectrum antibiotics according to the hospital protocol (penicillin 12 million units a day, clindamycin 600 mg four times a day and a single dose of 360 mg gentamicin). A peripheral blood smear was also done at admission, as shown in *figure 1*.

Figure 1. *Peripheral blood smear on admission*



WHAT IS YOUR DIAGNOSIS?

See page 423 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 422)

A BLOOD SMEAR ON ADMISSION

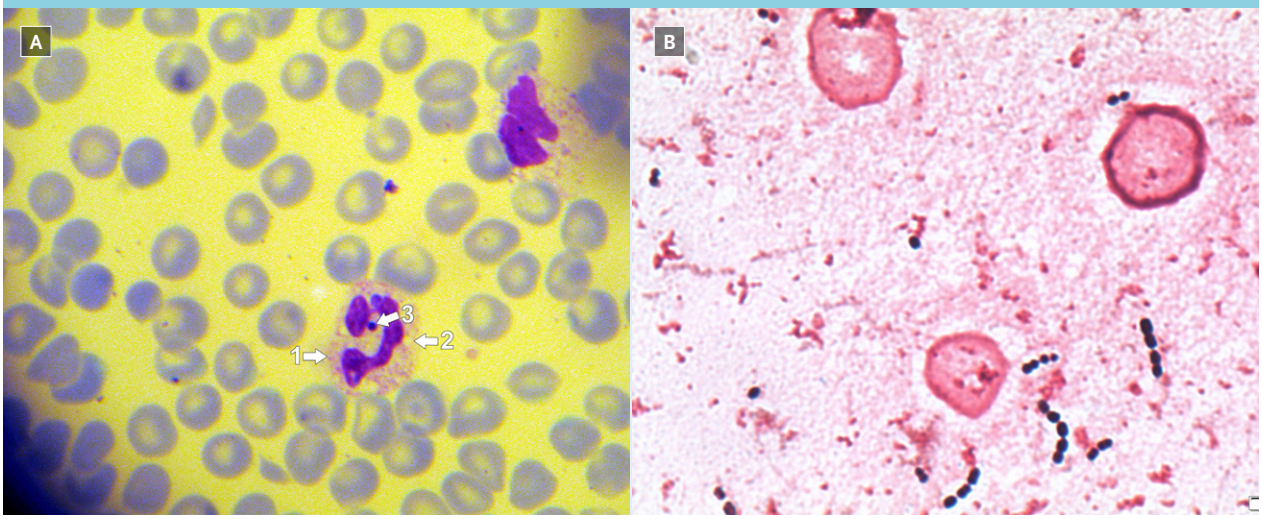
DIAGNOSIS

Figure 2 (*panel A*) shows the peripheral blood smear on admission, revealing neutrophils with morphological changes as seen in inflammation: toxic granulation, cytoplasmic vacuolation and possible phagocytised cell debris or apoptotic nucleus parts. We continued the broad-spectrum antibiotics. Later on, Gram staining of the incubated blood cultures showed Gram positive diplococci (*figure 2, panel B*). Definitive culture results diagnosed our patient with a *Streptococcus pneumoniae* sepsis and multi-organ failure, with disseminated intravascular coagulation, rhabdomyolysis and anuric acute kidney injury. Her condition worsened shortly after ICU admission, and she was treated with mechanical ventilation, fluid resuscitation, noradrenaline, milrinone and continuous venovenous haemofiltration. We continued the penicillin for a total of ten days. She completely recovered.

Streptococcus pneumoniae infection is common in patients above the age of 65 years. The incidence of invasive pneumococcal disease in the Netherlands is around 15 per 100,000 inhabitants (2500 new infections per year). Approximately 300 patients die due to invasive pneumococcal disease, another 75-100 have severe morbidity.[1]

Neutrophils are one of the most important innate defence mechanisms against bacteria. They rapidly migrate to sites of colonisation and infection, where antimicrobial mechanisms (degranulation with release of antimicrobial proteins and release of neutrophil extracellular traps) and phagocytosis can then take place.[2,3] Toxic granulation and cytoplasmic vacuolation are morphological changes that occur in the circumstances of bacterial infection, with other causes of inflammation or after administration of granulocyte colony stimulation factor. Predicting bacterial infections based on these morphological changes has been described in the past.[4] The prognostic value of these findings is unclear. One study reports lower mortality in septic patients when neutrophils show higher phagocytic activity.[5] However, excessive neutrophil migration to sites of inflammation can result in detrimental damage to surrounding tissues. To reduce this damage, the duration of neutrophil recruitment and toxic changes is regulated through anti-inflammatory and pro-resolving processes.[3] Though not commonly used as a diagnostic tool, a peripheral blood smear can provide 'circumstantial' evidence of bacteraemia, before definitive proof by blood cultures is obtained: toxic granulation and cytoplasmic vacuolation in neutrophils, and in some cases even free circulating and phagocytised bacteria.[6]

Figure 2. *Panel A: Peripheral blood smear on admission, showing neutrophils with morphological changes: toxic granulation (arrow 1), cytoplasmic vacuolation (arrow 2) and possible phagocytised cell debris or apoptotic nucleus parts (arrow 3). Panel B: Gram staining of the incubated blood cultures, showing Gram positive diplococci*



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