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"A worm emerging from the foot: what is your diagnosis?"

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EDITORAL

Impact and citations

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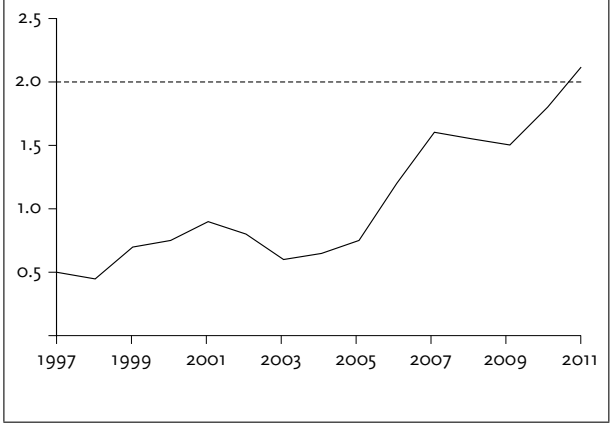
This summer Thomson Reuters released the Journal Citation Report 2011 containing the impact factors for 2011 of all international scientific journals and announced that the 2011 impact factor of the Netherlands Journal of Medicine was 2.1. For the first time in its history the Journal had crossed the almost magical boundary of 2.0. The Netherlands Journal of Medicine thereby occupies position 38 in the list of best medical journals in the world. The Netherlands Journal of Medicine belongs to the top-5 national medical journals, with only JAMA (United States), BMJ (United Kingdom), Journal of the Canadian Medical Association (JCMA), and Deutsches Arzteblatt International at higher positions. So, it has a higher rating than other national or regional-oriented journals such as the Scandinavian Journal of Medicine, European Journal of Internal Medicine, and Swiss Medical Journal. Interestingly, the top medical journals are often general journals and have relatively higher impact factors than journals in subspecialties.[1]

The rise in impact factor of the Netherlands Journal of Medicine is a steady process that started many years ago (*figure 1*). It is evident that already under the Nijmegen editorship an increasing trend started, which has been sustained over recent years. The impact factor of a journal in a given year is based on the number of citations to articles in that journal that have been published in the preceding two years.[2] Hence, the impact factor of 2011 is based on citations in 2011 to papers published in 2009 and 2010. *Table 1* shows the best-cited papers that were published in the Netherlands Journal of Medicine in 2010. Most of these papers are review manuscripts that traditionally attract more attention and citations than other types of paper. However, some of the case reports (of which the Journal publishes only a relatively small number) also received a lot of citations (*table 2*). It should be remembered, however, that in this calculation only the most immediate citations (i.e. of papers in the last two years) are considered and that papers that generate interest after a longer interval or remain interesting and generating citations over a longer period are not taken into account. Another JCR parameter, the cited half-life, provides a better reflection of more long-time citations to an article (the period in which half of the citations were generated). The cited half-life of the Netherlands Journal of Medicine in 2011 was 5.9 and also shows an increasing trend. As citation analysis in itself is not perfect, other methods to assess the scientific status of journals have also been proposed.[3-5]

Figure 1. *Impact factor of the Netherlands Journal of Medicine*



A higher impact factor generally leads to more submissions. Indeed, the number of submissions to the Netherlands Journal of Medicine has shown a steep upward trend in recent years.[6] This may imply that more authors are considering sending their work to our Journal and that the editors have a better choice of high-quality papers. A higher quality of published work will subsequently lead to more citations and a better impact factor. Hence, these positive feedback mechanisms cause a certain self-propelling force once a threshold has been passed. On the other hand, a host of new medical journals have appeared in recent years, thereby seriously diluting the impact a single journal can have. Also, since the number of pages of the Journal is more or less fixed,

Table 1. *Top 10 most cited papers of 2010*

Anas AA, et al. Recent insights into the pathogenesis of bacterial sepsis[7]
Lowenberg EC, et al. Platelet-vessel wall interaction in health and disease[8]
Nanayakkara PWB, et al. Vascular disease and chronic renal failure[9]
Levi M, et al. Bleeding in patients using new anticoagulants[10]
Seger RA. Chronic granulomatous disease: recent advances[11]
Kars M, et al. Update in prolactinomas[12]
Delsing CE, et al. Q fever in the Netherlands from 2007-2010[13]
Aslami H, et al. Induction of a hypometabolic state during critical illness[14]
Biere-Rafi S, et al. Effect of haemophila and von Willebrand disease on thrombosis[15]
Verhave G, et al. Role of vitamin D in cardiovascular disease[16]

Table 2. *Top 5 most cited case reports of 2010*

Chen Z, et al. Hepatic veno-occlusive disease associated with herbal preparations[17]
Chen SZ, et al. Rhabdomyolysis following pandemic influenza A[18]
Houwert AC, et al. Hereditary persistence of alpha-fetoprotein[19]
Haringhuizen A, et al. Fatal cerebral oedema in adult diabetic ketoacidosis[20]
Netea MG, et al. Chronic yersioniosis due to defects in TLR5 and NOD2 pathways[21]

more submissions will result in a lower acceptance rate of submitted papers. In fact, for some categories the acceptance rate in the Netherlands Journal of Medicine is already quite low.[6]

Taken together, the editors of the Netherlands Journal of Medicine are proud of its recent impact factor and would like to thank all authors who have sent excellent contributions to the Journal as well as our reviewers and associate editors, who have done a superb job in assisting us in selecting the best manuscripts and providing advice on improvement of manuscripts that were considered for publication. We will do our best to keep the esteem and the impact factor of the Netherlands Journal of Medicine as high as we can in the years to come.

REFERENCES

1. Levi M. Generalism of journals of internal medicine. Neth J Med. 2011;69:478-9.
2. Levi M. Impact of articles reflected by the journal's impact factor. Neth J Med. 2011;69:300-1.
3. Opthof T. Sense and nonsense about the impact factor. Cardiovasc Res. 1997;33:1-7.
4. Leydesdorff L. Alternatives to the journal impact factor: I3 and the top-10% (or top-25%?) of the most-highly cited papers. Scientometrics. 2012;92:355-65.
5. Weale AR, Bailey M, Lear PA. The level of non-citation of articles within a journal as a measure of quality: a comparison to the impact factor. BMC Med Res Methodol. 2004;4:14.
6. Levi M. Submission, acceptance, citation and download of articles in the Netherlands Journal of Medicine. Neth J Med. 2010;68:332-5.
7. Anas AA, Wiersinga WJ, de Vos AF, van der Poll T. Recent insights into the pathogenesis of bacterial sepsis. Neth J Med. 2010;68:147-52.
8. Lowenberg EC, Meijers JC, Levi M. Platelet-vessel wall interaction in health and disease. Neth J Med. 2010;68:242-51.
9. Nanayakkara PW, Gaillard CA. Vascular disease and chronic renal failure: new insights. Neth J Med. 2010;68:5-14.
10. Levi MM, Eerenberg E, Lowenberg E, Kamphuisen PW. Bleeding in patients using new anticoagulants or antiplatelet agents: risk factors and management. Neth J Med. 2010;68:68-76.
11. Seger RA. Chronic granulomatous disease: recent advances in pathophysiology and treatment. Neth J Med. 2010;68:334-40.
12. Kars M, Dekkers OM, Pereira AM, Romijn JA. Update in prolactinomas. Neth J Med. 2010;68:104-12.
13. Delsing CE, Kullberg BJ, Bleeker-Rovers CP. Q fever in the Netherlands from 2007 to 2010. Neth J Med. 2010;68:382-7.
14. Aslami H, Juffermans NP. Induction of a hypometabolic state during critical illness – a new concept in the ICU? Neth J Med. 2010;68:190-8.
15. Biere-Rafi S, Zwiers M, Peters M, van der Meer J, Rosendaal FR, Buller HR. The effect of haemophilia and von Willebrand disease on arterial thrombosis: a systematic review. Neth J Med. 2010;68:207-14.
16. Verhave G, Siegert CE. Role of vitamin D in cardiovascular disease. Neth J Med. 2010;68:113-8.
17. Chen Z, Huo JR. Hepatic veno-occlusive disease associated with toxicity of pyrrolizidine alkaloids in herbal preparations. Neth J Med. 2010;68:252-60.
18. Chen SC, Liu KS, Chang HR, Lee YT, Chen CC, Lee MC. Rhabdomyolysis following pandemic influenza A (H1N1) infection. Neth J Med. 2010;68:317-9.
19. Houwert AC, Giltay JC, Lentjes EG, Lock MT. Hereditary persistence of alpha-fetoprotein (HPAF P): review of the literature. Neth J Med. 2010;68:354-8.
20. Haringhuizen A, Tjan DH, Grool A, van Vught R, Van Zanten ARH. Fatal cerebral oedema in adult diabetic ketoacidosis. Neth J Med. 2010;68:35-7.
21. Netea MG, van der Leij F, Drenth JP, et al. Chronic yersiniosis due to defects in the TLR5 and NOD2 recognition pathways. Neth J Med. 2010;68:310-5.

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REVIEW

New trends in the prevention and management of community-acquired pneumonia

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ABSTRACT

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality worldwide. This review summarises current trends and knowledge gaps in CAP management and prevention. Although *Streptococcus pneumoniae* is the most frequent cause of CAP, identification of the microbial cause of infection remains unsuccessful in most episodes, and little is known about the aetiology of CAP in immunocompromised patients. Urinary antigen testing has become standard care for diagnosing Legionella infection, and pneumococcal urinary antigen testing is now recommended in the Dutch guidelines to streamline antibiotic therapy in patients hospitalised with CAP. In primary care C-reactive protein determination is recommended to improve antibiotic prescription for lower respiratory tract infections. In patients hospitalised with CAP, three strategies are considered equally effective for choosing empirical antibiotic treatment. Yet, more (and better designed) studies are needed to determine the best strategy, as well as to determine optimal (which usually means the minimum) duration of antibiotic therapy and the role of adjuvant treatment with corticosteroids. The effectiveness of the 23-valent pneumococcal polysaccharide vaccine in preventing invasive pneumococcal disease and pneumococcal CAP remains debated, and whether the newer conjugate vaccines are more effective remains to be determined. Many of these questions are currently being addressed in large-scaled trials in the Netherlands, and their results may allow evidence-based decisions in CAP management and prevention.

KEYWORDS

Community acquired pneumonia, immunisation, empirical antibiotic therapy, corticosteroids

INTRODUCTION

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality worldwide.[1-3] Reported annual incidences differ between countries, probably reflecting heterogeneity of diagnostics, reporting and socioeconomic factors.[4] A universal finding, however, is that *S. pneumoniae* is the most commonly identified bacterial pathogen for CAP in all age groups. The purpose of this review is to summarise new developments in the field of prevention and management of bacterial CAP, and to discuss potential consequences for the Netherlands.

MICROBIOLOGICAL AETIOLOGY OF CAP

Although many micro-organisms can cause CAP, most episodes are caused by a few pathogens only. *Table 1* displays proportions of pathogens documented in patients hospitalised with CAP in European countries, in which the diagnostic workup included blood cultures together with at least one other test, such as serology, polymerase chain reaction (PCR) for respiratory pathogens or urinary pneumococcal antigen testing. In most studies *S. pneumoniae* is the most frequently detected pathogen, accounting for 20-40% of CAP episodes. This proportion seems to be higher in studies from northern and western European countries compared with those from southern Europe. This may result from lower diagnostic sensitivity of blood and sputum cultures due to antibiotic use prior to hospital admission in southern countries.[5] Other common pathogens causing CAP include *Haemophilus influenzae, Mycoplasma pneumonia, Legionella pneumophila* and respiratory viruses. *Chlamydophila pneumoniae* and *Coxiella burnetii* are relatively rare causes of CAP, but may cause epidemics, as recently witnessed in the Netherlands during a Q-fever outbreak.[6-8]

Table 1. *Aetiology of CAP in hospitalised patients*

	The Netherlands 5 studies n=1047 (a)	Germany 1 study n=237 (b)	Switzerland 1 study n=318 (c)	United Kingdom 3 studies n=439 (d)	Southern Europe 19 studies n=9143 (e)	Slovenia 2 studies n=320 (f)	Nordic countries 7 studies n=1582 (g)
Streptococcus pneumoniae	31% (25-37)	13% (9-18)	13% (9-17)	35% (21-51)	23% (20-26)	9% (4-20)	30% (23-37)
Haemophilus influenzae	5% (3-10)	6% (4-10)	6% (4-9)	7% (5-10)	3% (2-4)	2% (1-7)	5% (4-8)
Staphylococcus aureus	1% (1-2)	4% (2-7)	4% (3-7)	2% (1-4)	1% (1-2)	1% (0-2)	1% (1-2)
Moraxella catarrhalis	1% (0-3)	-	2% (1-4)	2% (1-3)	0% (0-1)	1% (0-11)	1% (0-2)
Pseudomonas spp.	1% (0-3)	-	-	1% (0-3)	1% (0-2)	-	0% (0-1)
Klebsiella pneumoniae	0% (0-1)	-	1% (0-3)	1% (0-2)	0% (0-1)	-	1% (0-1)
Escherichia coli	1% (0-2)	-	-	1% (0-2)	1% (0-1)	2% (1-4)	1% (0-1)
Other gram-negatives	4% (1-12)	8% (6-13)	-	-	1% (1-2)	1% (0-3)	1% (1-3)
Mycoplasma pneumoniae	9% (4-16)	9% (6-14)	8% (5-11)	3% (2-6)	4% (3-7)	13% (3-43)	7% (5-10)
Chlamydophila pneumoniae	1% (0-3)	11% (8-16)	3% (1-5)	2% (0-24)	2% (1-5)	19% (15-24)	1% (0-3)
Chlamydophila psittaci	1% (0-4)	1% (0-3)	-	1% (0-4)	1% (0-1)	1% (0-3)	1% (0-2)
Coxiella burnetii	1% (0-1)	2% (1-5)	-	1% (0-2)	1% (1-2)	1% (0-2)	0% (0-1)
Legionella pneumophila	4% (3-7)	2% (1-4)	5% (3-8)	3% (2-5)	5% (4-7)	3% (1-5)	2% (1-3)
Viruses	9% (3-21)	10% (7-15)	-	16% (8-28)	4% (3-7)	5% (0-75)	10% (6-18)
Other agents	4% (2-8)	1% (0-3)	1% (0-3)	3% (0-6)	3% (2-5)	2% (0-8)	2% (1-5)
Unknown	36% (25-49)	33% (27-39)	61% (56-66)	40% (23-60)	44% (40-49)	43% (34-52)	38% (27-49)

A few studies included both general ward and ICU patients; complete references can be obtained from the authors. a) Boersma 1991[142], Bohte 1995[143], Braun 2004[144], Van der Eerden 2005[145], Snijders 2010[116]; b) Steinhoff 1996[146]; c) Garbino 2002[147]; d) Venkatesan 1990[148], Lim 2001[149], Howard 2005[150]; e) Levy 1988[151], Ausina 1988[152], Pachon 1990[153], Blanquer 1991[154], Almirall 2007[155], Pareja 1992[156], Falco 1991[157], Ruiz-Gonzalez 1999[158], Sopena 1999[159], Fernandez-Sabe 2003[160], Menendez 1999[161], Lorente 2000[68], Ruiz 1999[162], Cilloniz 2011[163], Zalacain 2003[164], Falguera 2001[165], Marcos 2003[166], Briones 2006[167], Angeles Marcos 2006[168]; f) Socan 1999[169], Beovic 2003[170]; g) Kerttula 1987[171], Holmberg 1987[172], Burman 1991[173], Ostergaard 1993[174], Stralin 2010[175], Hohenthal 2008[176], Johansson 2010[45].

In 30-60% of CAP episodes the aetiology remains unknown, and this proportion has remained unchanged over time, despite the introduction of antigen testing and PCR-based testing. This has been attributed to less microbiological testing in clinical care or increased use of antibiotics prior to diagnostic testing.[9] Therefore, although there are no discernible signs of major changes in the microbial aetiology of CAP over time, it is unknown whether such changes could have been masked by the suggested changes in clinical practice.

In addition the patient population affected is changing, with increasing numbers of severely immune-compromised patients, due to more frequent use of immune-modulating treatment modalities as well as to better survival of patients with serious illnesses.[10-12] These patients are prone to developing CAP with both common respiratory pathogens and opportunistic pathogens. Since these immunocompromised patients have been excluded in most studies, the prevalence of opportunistic pathogens such as *Pneumocystis jirovecii*, atypical mycobacteria and fungi may have been underestimated. Among HIV-infected patients hospitalised with CAP, the reported prevalence of *P. jirovecii* has ranged from 9-31% and of *Mycobacterium species* from 1-17% of cases, which occurred in addition to pathogens common in immunocompetent populations.[13-17] Few data are available on CAP aetiology in patients with other types of immunosuppression, although Gram-negative bacteria and fungal infections have been reported in small case series.[18-21] Summarising, the aetiology of CAP in immunocompetent patients seems unchanged with *S. pneumonia* remaining most prevalent, but less is known about pathogen distribution in the growing population of immunocompromised patients.

DIAGNOSTICS AND MANAGEMENT OF CAP IN PRIMARY CARE

Most patients with CAP are treated in primary care settings, with reported annual incidences (based on the International Classification of Primary Care) of 7.0 /1000 patients in 2009.[22] General practitioners (GP) must rely on clinical signs and symptoms to diagnose lower respiratory tract infections (LRTI) and CAP. As a consequence, the microbial aetiology of infection is seldom established. In studies with a standardised microbiological work-up, 13-65% of LRTI episodes were caused by respiratory viruses, mostly influenza and rhinoviruses, and the most frequent bacterial causes of infection were *S. pneumoniae, H. influenzae* and *M. pneumoniae*. As in hospitalised patients, no pathogen was detected in 40-60% of episodes.[23-25]

Consequently, treatment decisions in primary care are almost always empiric, and identification of patients at risk for a complicated course of disease or death is important. Among 315 elderly patients with CAP diagnosed in primary care in the Netherlands, 7% were referred to hospitals upon first presentation and 15% within 30 days.[26] Age and presence of comorbidity, especially cardiovascular diseases and diabetes, are predictors for death or need of hospitalisation within 30 days after diagnosis of LRTI.[27,28] The Guidelines of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG), therefore, recommend antibiotic treatment for these high-risk patients.[29] Yet, antibiotics remain overprescribed, either because of the GP's previous experiences and beliefs or concerns about the severity of the disease, or the (GP's perception of) patient's expectations.[30-32]

In 13 European countries, the proportion of antibiotic prescriptions for LRTI in primary care ranged from 20% in Spain to almost 90% in Slovakia, and was 42% in the Netherlands.[33]

Although antibiotic resistance among respiratory pathogens is low, 11.5% and 7% of *S. pneumoniae,* isolated from primary care and hospital settings, respectively, are currently resistant to doxycycline.[34] For this reason amoxicillin is now recommended as first-choice treatment of LRTI and CAP in primary care.[29]

Education of GPs and patients has been proposed as a means to improve antibiotic prescription in primary care. GP group education meetings, to improve knowledge of guidelines, and communication techniques aiming at better agreement with patients' expectations had different success rates.[31,35] Furthermore, point-of-care determination of the C-reactive protein (CRP) blood level may assist in distinguishing high- and low-risk patients when clinical signs and symptoms of CAP are not conclusive.[36] CRP point-of-care testing has now been incorporated in a decision tree for antibiotic treatment in the NHG guideline for LRTI.[29] Implementation of CRP point-of-care testing in primary care is currently being evaluated in the 'CRP Rapid Testing in Adults and Children in Primary Care' (CaTCH) study. Furthermore, antibiotic prescription could be improved through better determination of the microbial causes of LRTI.[24] Whether a combined approach of GP education, training in patient communication techniques and implementation of point-of-care tests is a cost-effective manner to reduce overprescription of antibiotics for LRTI in primary care remains to be determined.

DIAGNOSTICS AND MANAGEMENT IN SECONDARY CARE

Establishing a microbiological diagnosis of CAP still relies predominantly on the traditional culture techniques introduced by Koch and Pasteur in the 19th century. Yet, there is an urgent need for more precise and more rapid diagnostic tests in order to guide targeted antibiotic treatment and to prevent unnecessary use of antibiotics.[9] In this respect, urinary antigen testing for Legionella and pneumococci, procalcitonin-based guidance of antibiotic therapy, and PCR-based testing of respiratory samples and whole blood have been evaluated.

Urinary antigen testing

The immunochromatographic membrane assays Binax Now (Binax) can detect *L. pneumophila* type I antigen or capsular polysaccharide antigens of *S. pneumonia* in urine.[37] The test for Legionella has a high sensitivity for type I species (70-100%, with higher sensitivity for severe CAP) and high specificity (95-100%).[37-39] Legionella serotype I accounts for 90% of all infections caused by Legionella. The current Dutch guideline recommends to test for Legionella antigens in urine within 12 hours in patients with moderately severe CAP.[40]

For the pneumococcal urinary antigen test, reported specificities and sensitivities ranged from 90-100% and from 50-80%, respectively, depending on the reference standards that were used.[41-49] The pooled positive predictive value of 20 studies was 79% (95% CI 70-88%) with a pooled negative predictive value of 92% (95% CI 89-96%).[50] False-positive results may occur in children and COPD patients due to extensive colonisation with pneumococci, or after recent pneumococcal infection, as antigens may remain detectable for months.[51] The sensitivity of this test is much more difficult to determine, especially in patients with non-bacteraemic episodes of pneumococcal CAP. In patients with bacteraemic pneumococcal CAP, though, 15-20% had negative urinary antigen tests, which might result from sequestration of antigen-antibody immune complexes with decreased antigen shedding in the urine.[50] The positive predictive value of this test might be used to de-escalate initial broad-spectrum antibiotic therapy to a more narrow-spectrum treatment with penicillin or amoxicillin.[40,52,53]

Procalcitonin

Procalcitonin (PCT), a precursor of calcitonin, is a soluble protein that can be elevated in plasma during bacterial infection, sepsis and severe inflammatory reactions such as pancreatitis.[54] PCT levels might be used to reduce total antibiotic exposure in patients with CAP. There have been four randomised trials comparing PCT-guided antibiotic treatment to standard care in patients hospitalised with CAP.[55-58] In the first study a PCT-based approach reduced antibiotic use by 49% in patients admitted with suspected LRTI. The major effects were achieved in patients with a clinical diagnosis of acute

bronchitis.[55] In subsequent studies daily PCT monitoring reduced the median length of antibiotic treatment from 12 to five days in a single-centre study and from 8.7 to 5.7 days in a multicentre study.[56,58] In a fourth study a single PCT measurement at admission reduced the mean length of antibiotic treatment from 6.8 to 5.1 days, with equal proportions of patients starting with antibiotics at admission.[57]

Yet, the optimal duration of antibiotic treatment for CAP is unknown. In two randomised trials treatment of five and seven days (with a fluoroquinolone or with a macrolide) had comparable clinical efficacies.[59,60] In a Dutch study on hospitalised patients with mild or moderate-to-severe CAP (PSI score ≤110), who had significantly improved within three days after start of antibiotic treatment, clinical outcome was comparable for those patients who were randomised to discontinuation of antibiotic therapy after day 3 and those who continued antibiotics for five more days.[61] PCT was not used in any of these studies. The Dutch guideline now recommends to treat mild and moderately severe CAP for five days, when using a betalactam or quinolone antibiotic.[40] Furthermore, patients can safely switch from intravenous to oral antibiotics as soon as clinical improvement occurs (e.g. decrease in fever and respiratory rate, haemodynamic stability).[40] Whether PCT measurement can further reduce antibiotic use in the Netherlands remains to be determined.

Nucleic acid amplification tests

Detection of microbial nucleic acid with nucleic acid amplification tests such as PCR in respiratory samples or blood may overcome the problem of culture-negative results after antibiotic therapy, and the inherent diagnostic delay of culture procedures and susceptibility testing. Real-time PCR combines amplification and detection in one reaction (reducing cross-contamination) and allows quantification of the infection load. Multiplex systems allow identifying multiple pathogens within the same time and in a single specimen.

PCR for specific pathogens

PCR is commonly used for certain respiratory viral pathogens (e.g. influenza, RSV, hMPV), but not yet for bacterial pathogens. PCR-based tests for *S. pneumoniae* have relied on the amplification of three different gene targets: pneumolysin, autolysin, and the DNA-fragment Spn9802.[62] The last two seem to be more sensitive and cross-reactions with other streptococcal species can occur with pneumolysin.[62-65] Reported sensitivity and specificity of PCR-based tests for *S. pneumoniae* in respiratory samples were 79% and 88%, respectively, and antibiotic therapy of less than 24 hours did not reduce sensitivity.[64,66] As with culture techniques, PCR results cannot distinguish between colonisation and infection, although quantification of bacterial DNA load or relating this to the number of human epithelial cells may help in doing so.[67]

Direct testing of blood samples with PCR-based tests for *S. pneumonia* had reported sensitivities of 50-70% and specificities of 90-100% when compared with blood culture results.[62,68,69] The true sensitivity, though, might be higher than for culture-based methods, but this is difficult to determine in the absence of a reliable reference standard. Yet, false-positive results can also occur and might be related to contamination or extensive pneumococcal colonisation.[68] In bacteraemic patients, increased pneumococcal DNA loads in blood have been associated with increased mortality, need for mechanical ventilation and increased length of hospital stay.[70,71] The clinical consequences of these tests remain to be determined. In one study of bacteraemic patients, pneumococcal urinary antigen testing appeared to be more sensitive, cheaper and less labour intensive than PCR-based testing of blood.[69]

PCR has wider applications for 'difficult to culture' respiratory pathogens, such as *Mycoplasma pneumoniae, Legionella* species, *Chlamydophila pneumoniae, Bordetella pertussis, P. jiroveci* and *M. tuberculosis*.[72-75] For the diagnosis of acute Q fever, PCR of *Coxiella burnetii* can be used during the first three weeks after symptoms have started.[76]

Up till now, large clinical validation studies for the use of PCR-based tests of respiratory samples in CAP diagnosis and management are lacking. In the only randomised controlled trial, a real-time multiplex PCR for respiratory viruses and atypical pathogens was evaluated in two Dutch hospitals. The test was associated with a higher diagnostic yield, but did not reduce antibiotic use and increased health care costs.[77]

Management of CAP in secondary care

As the microbiological cause of CAP cannot be predicted reliably on clinical symptoms, guidelines recommend basing initial treatment choices on the severity of disease presentation.[40,78,79] Patients with mild diseases can be treated with narrow-spectrum antibiotics (always covering *S. pneumonia*e) with careful monitoring of treatment response within 48 hours. On the other hand, in those with severe CAP a broader spectrum is recommended that includes at least *S. pneumonia* and Legionella. In those with moderately severe CAP, empirical coverage of *S. pneumonia* is always needed, but coverage of Legionella can be based on the results of urinary antigen testing in most patients. Dutch guidelines recommend to use either of three scoring systems: the CURB-65-score, the Pneumonia Severity Index score (PSI) or the pragmatic classification.[80,81] The contents of the three severity classification systems and the recommendations for empirical treatment have been

discussed in this journal recently.[40] They are, therefore, summarised in *Box 1*.

Current guideline recommendations are based on non-experimental cohort studies only and have, therefore, been criticised.[82-84] Some studies suggest that combined treatment with a β-lactam antibiotic and macrolide improves outcome as compared with monotherapy with a β-lactam antibiotic,[85-91] and some suggest that such combination therapy improves survival in pneumococcal pneumonia.[92-95] On the contrary, other studies failed to demonstrate beneficial effects of combination therapy (versus β-lactam monotherapy) on patient outcome.[96-102] Better results of regimens that combine a macrolide and β-lactam antibiotic or in which fluoroquinolones are used as monotherapy might result from coverage of atypical pathogens, less resistance, synergy between β-lactams and macrolides, and anti-inflammatory effects of macrolides.[103] A major pitfall for observational studies is *confounding by indication,* which arises when factors contributing to the endpoint differ between treatment groups because of the physician's treatment decision.[104] For instance, patients who received combination therapy might have had a higher suspicion of atypical pathogens because they were younger, and therefore, had a better prognosis. In several of the aforementioned cohort studies, either with or without beneficial effects for combination therapy, there is clear evidence of such confounding bias.[85,87,88,91,92,96,97] This was elegantly demonstrated in one study by using a propensity analysis to predict treatment on the basis of clinical variables. These propensity scores differed significantly between treatment groups and the benefit of combination therapy in the crude analysis disappeared after adjustment for the propensity score in multivariate analysis.[101]

As a result the relative effectiveness of empirical treatment of CAP with β-lactam monotherapy, combination therapy with a β-lactam and macrolide, or fluoroquinolone monotherapy is unknown. This is addressed in a multicentre cluster randomised cross-over trial in seven Dutch hospitals (CAP-START study, http://clinicaltrials.gov/ct2/show/NCT01660204). In each hospital one of the three treatment regimens will be used as standard empirical therapy during a period of four consecutive months, after which preferred treatment changes to one of the other two regimens. The order of regimens is randomised per hospital to control for inter-hospital variables and seasonal effects.

Box 1. *Current guideline recommendations for treatment of CAP*

***Mild CAP**
CURB-65: 0-1
PSI: 1-2
Pragmatic: Ambulatory treatment
Recommendation for empirical treatment:
Amoxicillin, second choice doxycycline

***Moderately severe CAP**
CURB-65: 2
PSI: 3-4
Pragmatic: Treatment on hospital ward (non-ICU wards)
Recommendation for empirical treatment:
Amoxicillin (if no risk factors for Legionella infection and with a urinary Legionella antigen test to be done within 12 hours).

***Severe CAP**
CURB-65: >2
PSI: 5
Pragmatic: Treatment in ICU ward
Recommendation for empirical treatment:
Moxifloxacin or levofloxacin, penicillin/ amoxicillin with ciprofloxacin, or 2nd or 3rd generation cephalosporin with a macrolide

CORTICOSTEROIDS AS ADJUNCTIVE TREATMENT OF CAP

Morbidity and mortality of patients hospitalised with CAP has been attributed to an imbalanced immune response yielding organ failure and septic shock.[105] These detrimental effects could be modulated through corticosteroids, as has been demonstrated in patients with bacterial meningitis and vasopressor-dependent septic shock.[106,107] In CAP patients without septic shock, however, the benefits of corticosteroids added to antibiotic treatment are less obvious.[108-110] This approach has been evaluated in six randomised trials,[111-116] four of which had less than 50 patients (*table 2*). In the largest study (304 patients) four days of dexamethasone 5 mg was associated with a median reduction in hospital stay of one day (95% CI 0-2 days) in patients hospitalised with CAP not requiring immediate ICU admission. However, patients requiring ICU admission after several days in hospital were excluded from analysis. The other large study (213 patients) failed to demonstrate significant reductions in length of stay or mortality in patients randomised to additional treatment with seven days of prednisolone 40 mg versus placebo. Based on these two studies there is no clear evidence that adjunctive treatment with corticosteroids is beneficial in patients with CAP in the absence of septic shock. The effects of corticosteroids as an adjunct to antibiotic therapy

Table 2. *Randomised controlled trials on corticosteroids in CAP*

Study	Marik 1993[113]	Confalonieri 2005[111]	Mikami 2007[115]	Snijders 2010[116]	Fernàndez 2011[112]	Meijvis 2011[114]
Country	South Africa	Italy	Japan	Netherlands	Spain	Netherlands
N	30	46	31	213	45	304
Design	Open label placebo-controlled RCT	Double-blind placebo-controlled RCT; treating physician not blinded	Open label RCT	Double-blind placebo-controlled RCT	Double-blind placebo-controlled RCT	Double-blind placebo-controlled RCT
Intervention	Hydrocortisone 10 mg/kg single dose	Hydrocortisone bolus 200 mg + 240 mg 7 days	Prednisolone 40 mg 3 days	Prednisolone 40 mg 7 days	Methyl-prednisolone bolus 200 mg + schedule§	Dexamethasone 5 mg 4 days
Setting	ICU	ICU	General ward¶	Hospital (10% ICU)	Hospital (16% ICU)	General ward¶
Age mean (SD)	36.4 (13.9)	63.5 (16.1)	72.0 (19.5)	63.5 (18.3)	63.6 (NR)	63.6 (18.5)
PSI classification	NR	NR	I: 3 (10%) II: 2 (6%) III: 9 (29%) IV: 14 (45%) V: 3 (10%)	I: 28 (13%) II: 43 (20%) III: 49 (23%) IV: 63 (30%) V: 30 (14%)	I: 0 (0%) II: 4 (9%) III: 13 (29%) IV: 25 (56%) V: 2 (4%)	I: 40 (13%) II: 64 (21%) III: 57 (18%) IV: 97 (32%) V: 46 (15%)
Mortality RR (95% CI)	0.38 (0.05-3.26)[A]	0.07 (0.004-1.10)[B ‡]	NR	1.05 (0.33-3.37)[CD] 0.76 (0.36-1.60)[CE]	0.96 (0.06-14.4)[B]	0.83 (0.35-1.94)[C]
Length of stay diff. (95% CI)	-0.3 (-4.0 to 3.4)	-8 (p=0.03) [F]	-8.7 (-18.9 to 1.5)[G] -0.3 (-3.6 to 3.0)[H]	-0.56 (-4.0 to 2.8)[D] -0.40 (-4.0 to 3.2)[E]	-2 (ns) [I]	-1 (-2 to 0)[J]
Comments	Patients with septic shock not excluded	Patients with septic shock not excluded				

PSI=Pneumonia Severity Index; ICU=intensive care unit; CI=confidence interval; NR=not reported; ¶patients admitted to the ICU on day 1 were excluded; §20 mg/6 h for 3 days + 20 mg/12 h for 3 days + 20 mg/24 h for 3 days; ‡p=0.009 (Fisher's exact test); seven patients died in the placebo group versus no patients in the intervention group; [A]ICU mortality; [B]In-hospital mortality; [C]30-day mortality; [D]Intention to treat analysis; [E]Per protocol analysis; [F]Difference in medians, no confidence interval reported; [G]PSI IV-V (n=17); [H]PSI I-III (n=14); [I]No significant difference, CI of difference cannot be retrieved. [J]Difference in medians.

is currently being evaluated in two placebo-controlled trials, one in Switzerland aiming to include 800 patients hospitalised with CAP (http://clinicaltrials.gov/ct2/show/NCT00973154) and one in Spain targeting for 120 CAP patients with PSI class V (http://clinicaltrials.gov/ct2/show/NCT00908713).

PREVENTION OF CAP BY PNEUMOCOCCAL IMMUNISATION

Based on differences in polysaccharide capsules, 91 different serotypes of *S. pneumonia* have been identified. Capsule polysaccharides have antiphagocytic activity, and are therefore relevant in the pathogenesis of CAP and invasive pneumococcal diseases (IPD).[117] As a result, incidence of IPD, clinical outcome after infection and age distribution differ between serotypes.[118-121]

The first human experiment of pneumococcal vaccination, based on administration of a mixture of polysaccharides, was conducted in 1911, and the first hexavalent-vaccine was registered in 1946. However, these vaccines were soon withdrawn because of the discovery of penicillin.[122] In the late 1970s, a 14-valent pneumococcal polysaccharide vaccine (PPV) was registered in the United States, which was replaced by a 23-valent PPV (Pneumovax/ Pneumo 23) in 1983, containing purified capsular antigens from 23 serotypes that cover approximately 87% of the isolates causing IPD in adults in the Netherlands.[119] The vaccine induces T-cell independent B-cell responses, yielding antibodies in adults but not in young children. As immunological memory is not induced, revaccination needs to be repeated every five years. In the Netherlands, this vaccine is only recommended for patients with a high risk of IPD, such as those with (functional) asplenia, sickle cell anaemia and with liquor leakage or prior pneumococcal meningitis after skull trauma.[123] For patients with immune suppression due to (non)-Hodgkin's disease, HIV or organ transplantation, immunisation is not strictly recommended, but can be applied.

Despite its use in many countries worldwide, the efficacy of the 23-PPV remains debated. Based on a recent meta-analysis quantifying combined risk ratios (based on a random-effects model) of (quasi)randomised studies,

PPV did not prevent infection (presumptive pneumococcal pneumonia, all-cause pneumonia and death from all causes) in trials with a double-blind design and with adequate allocation of treatment.[124] Also the risk ratio of pneumococcal bacteraemia was close to one (RR 0.90 (0.46-1.77)), even without trial quality taken into account. These findings differ markedly from the reported effect of PPV on the occurrence of IPD (OR 0.26, 95% CI 0.15-0.46) based on ten studies in the most recent Cochrane review.[125] Yet, only five trials were included in both analyses. The different outcomes result from differences in study selection, illustrating the large variety in study populations and outcome definitions. Large randomised controlled trials are lacking and interpretation of observational studies suffers from the 'healthy vaccinee' effect, which implies that subjects who have access to vaccination are usually in a better health condition than those who do not receive vaccination. Furthermore, there is no evidence that PPV prevents IPD in patients with chronic underlying medical illnesses. Therefore, we concur with the conclusion reached by the Dutch Health Council in 2003 that there is no convincing evidence that PPV prevents pneumonia or IPD in adults and that PPV vaccination, as an adjunct to annual influenza vaccination, is not recommended.[123]

Since the turn of the century, pneumococcal conjugate vaccines (PCV) are available, with either seven (serotypes 4,6B, 9V, 14, 18C, 19F, 23F), ten (additional serotypes 1,5, 7F) or 13 (additional serotypes 3, 19A, 6A) polysaccharide capsular antigens conjugated to a protein. The last mentioned induces T-cell dependent immune responses, yielding adequate antibody responses in adults and young children, and immunological memory. The efficacy of conjugated pneumococcal vaccines in preventing pneumococcal disease in young children has been well established, with estimated vaccine efficacies of 80% (95% CI 58-90%) and 27% (95% CI 15-36%) for vaccine type IPD and X-ray confirmed pneumonia, respectively.[126] Moreover, in the United States introduction of PCV-7 vaccination among children was associated with declines in IPD rates in the elderly, presumably because of vaccine-induced herd immunity.[127] Conjugated vaccines have now been implemented in national immunisation programs for children across the world.[128-132]

In the Netherlands PCV-7 was introduced in the national immunisation program ('Rijks Vaccinatie Programma') in 2006, and was replaced by a ten-valent vaccine in 2011. Incidences of vaccine-serotype IPD in children <2 years had declined by 67% in 2008 (from 24.3 in 2005 to 8.0 cases/ 100,000 persons), but at that time, vaccine-serotype specific as well as overall IPD rates had not declined significantly among the elderly.[133]

In adults, a single dose of PCV-7 yields higher or at least equal immune responses to a single dose of 23-PPV, both in immune-competent and in immune-compromised adults.[134-138] Since October 2011, PCV-13 has been licensed for prevention of IPD in adults aged >50 years in Europe. A model-based cost-effectiveness analysis suggests that in the United States replacement of 23-PPV vaccination with PCV-13, either at the age of >65 years – as currently recommended in the US – or routinely at the age of 50 and 65 years might reduce pneumococcal disease burden in an economically acceptable way, but model estimates were critically sensitive to vaccine efficacy in prevention of non-bacteraemic pneumococcal CAP and the magnitude of herd immunity created by children's vaccination.[139] Up till now, effectiveness of PCV-7 vaccination in adults has only been determined in HIV-infected patients who had recovered from IPD in Blantyre, Malawi.[140] After a median follow-up of 1.2 years unadjusted vaccine efficacy to prevent a new episode of vaccine serotype IPD (PCV-7 serotypes + serotype 6A) was 74% (95% CI 30-90%), but there were no significant beneficial effects on all-cause IPD (adjusted HR 0.80 (95% CI 0.45-1.44)) or mortality (adjusted HR 1.24 (95% CI 0.88-1.75)). The effectiveness of PCV in preventing bacteraemic and non-bacteraemic CAP in immune-competent elderly is unknown. This is being addressed in an ongoing placebo-controlled double-blind trial evaluating the efficacy of PCV-13 in 84,496 elderly (>65 years) in the Netherlands.[141] (http://clinicaltrials.gov/ct2/show/NCT00744263) The results of this study are expected in 2013.

CONCLUSION

We have reviewed some, but certainly not all, trends and controversies in the diagnosis, management and prevention of CAP. The most important trends and knowledge gaps for the prevention and management of CAP are summarised in *table 3 (see page 344)*. Our daily clinical approach in patients with CAP has changed considerably in some aspects, such as the general approach to base empirical treatment on the severity of disease presentation rather than on the presumed involved pathogens, the frequent use of urinary antigen testing for Legionella and the shorter duration of (intravenous) antibiotic treatment. In other respects changes have not (yet) occurred, such as determination of microbial aetiology, defining optimal antibiotic strategies and duration of therapy, prevention through vaccination and the use of immunomodulating therapy. Large and well-designed studies are under way, some of them being conducted in the Netherlands, which may change our practices in the near future.

Table 3. *New trends and current knowledge gaps in the management of CAP*

Topic	New trends	Current knowledge gaps
Microbiological aetiology	Larger role for opportunistic pathogens due to increasing number of immunocompromised patients.	Aetiology of CAP in immunocompromised hosts (except for HIV-patients).
Management in primary care	Implementation of point-of-care CRP test for LRTI in primary care.	Effectiveness of different methods for reducing antibiotic prescriptions for LRTI in primary care.
Management in secondary care	Streamlining broad-spectrum empirical antibiotic therapy based on pneumococcal antigen testing. Shorter duration of (intravenous) antibiotic treatment in mild to moderate-severe CAP.	Clinical relevance of PCR-based microbiological testing. Role of procalcitonin in reduction of antibiotic treatment duration. Added value of covering atypical pathogens in empirical treatment of moderate-severe CAP. Effectiveness of corticosteroids as an adjunct to antibiotic therapy
Prevention	Pneumococcal conjugate vaccine introduced in Dutch national immunisation program for children aged 0-2 years. Pneumococcal conjugate vaccine available for elderly.	Effectiveness of pneumococcal polysaccharide and of conjugate vaccines in adults. Herd immunity effects of conjugate vaccination in children.

REFERENCES

1. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. JAMA. 2005;294:2712-9.
2. Oosterheert JJ, Bonten MJ, Hak E, Lammers JW, Schneider MM, Hoepelman IM. The increase in pneumonia-related morbidity and mortality among adults in the Netherlands and possible explanations for it. Ned Tijdschr Geneeskd. 20044;148:1765-9.
3. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67:71-9.
4. World Health Organisation. The global burden of diseases: 2004 update. WHO Press; 2008.
5. Goossens H, Ferech M, Coenen S, Stephens P. Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries. Clin Infect Dis. 2007;44:1091-5.
6. Dijkstra F, van der Hoek W, Wijers N, et al. The 2007-2010 Q fever epidemic in The Netherlands: characteristics of notified acute Q fever patients and the association with dairy goat farming. FEMS Immunol Med Microbiol. 2012;64:3-12.
7. Kauppinen MT, Herva E, Kujala P, Leinonen M, Saikku P, Syrjala H. The etiology of community-acquired pneumonia among hospitalized patients during a Chlamydia pneumoniae epidemic in Finland. J Infect Dis. 1995;172:1330-5.
8. Limonard GJ, Groot CA, Dekhuijzen PN, Nabuurs-Franssen MH. Coxiella burnetii: a genuinely novel causative agent of pneumonia in The Netherlands since May 2007. Epidemiol Infect. 2012;140:865-6.
9. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011;52(Suppl 4):S296-S304.
10. Martin-Mola E, Balsa A. Infectious complications of biologic agents. Rheum Dis Clin North Am. 2009;35:183-99.
11. Porter K, Babiker A, Bhaskaran K, et al. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. Lancet. 2003;362(9392):1267-74.
12. Ward EM, Thun MJ, Hannan LM, Jemal A. Interpreting cancer trends. Ann N Y Acad Sci. 2006;1076:29-53.
13. Camps SM, Cervera C, Pumarola T, et al. Virological diagnosis in community-acquired pneumonia in immunocompromised patients. Eur Respir J. 2008;31:618-24.
14. Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. Infection. 2008;36:231-6.
15. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med. 1995;152(4 Pt 1):1309-15.
16. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis. 2001;184:268-77.
17. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. AIDS. 2002;16:85-95.
18. Batlle M, Ribera JM, Oriol A, et al. [Pneumonia in patients with chronic lymphocytic leukemia. Study of 30 episodes). Med Clin (Barc). 2001;116:738-40.
19. Berman SJ, Johnson EW, Nakatsu C, Alkan M, Chen R, LeDuc J. Burden of infection in patients with end-stage renal disease requiring long-term dialysis. Clin Infect Dis. 2004;39:1747-53.
20. Hoyo I, Linares L, Cervera C, et al. Epidemiology of pneumonia in kidney transplantation. Transplant Proc. 2010;42:2938-40.
21. Lossos IS, Breuer R, Or R, et al. Bacterial pneumonia in recipients of bone marrow transplantation. A five-year prospective study. Transplantation. 1995;60:672-8.
22. Verheij RA, van Dijk CE, Abrahamse H, et al. Landelijk Informatienetwerk Huisartsenzorg. Feiten en cijfers over huisartsenzorg in Nederland. Utrecht/Nijmegen: NIVEL/IQ; 2009.
23. Holm A, Nexoe J, Bistrup LA, et al. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract. 2007;57(540):547-54.
24. Hopstaken RM, Stobberingh EE, Knottnerus JA, et al. Clinical items not helpful in differentiating viral from bacterial lower respiratory tract infections in general practice. J Clin Epidemiol. 2005;58:175-83.

25. Macfarlane J, Holmes W, Gard P, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. Thorax. 2001;56:109-14.

26. Bont J, Hak E, Hoes AW, Macfarlane JT, Verheij TJ. Predicting death in elderly patients with community-acquired pneumonia: a prospective validation study reevaluating the CRB-65 severity assessment tool. Arch Intern Med. 2008;168:1465-8.

27. Bont J, Hak E, Hoes AW, Schipper M, Schellevis FG, Verheij TJ. A prediction rule for elderly primary-care patients with lower respiratory tract infections. Eur Respir J. 2007;29:969-75.

28. Van de Nadort C., Smeets HM, Bont J, Zuithoff NP, Hak E, Verheij TJ. Prognosis of primary care patients aged 80 years and older with lower respiratory tract infection. Br J Gen Pract. 2009;59:e110-e115.

29. Verheij TJ, Hopstaken RM, Prins JM, et al. NHG Standaard Acuut Hoesten (Eerste herziening). Huisarts en Wetenschap. 2011;54(2):68-92.

30. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verheij TJ. Prescribing antibiotics for respiratory tract infections by GPs: management and prescriber characteristics. Br J Gen Pract. 2005;55:114-8.

31. Cals JW, Hopstaken RM, Butler CC, Hood K, Severens JL, Dinant GJ. Improving management of patients with acute cough by C-reactive protein point of care testing and communication training (IMPAC3T): study protocol of a cluster randomised controlled trial. BMC Fam Pract. 2007;8:15.

32. van Duijn HJ, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Illness behaviour and antibiotic prescription in patients with respiratory tract symptoms. Br J Gen Pract. 2007l;57:561-8.

33. Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. BMJ. 2009;338:b2242.

34. SWAB. Nethmap 2009 - Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in The Netherlands. 2009 Sep 21.

35. Smeets HM, Kuyvenhoven MM, Akkerman AE, et al. Intervention with educational outreach at large scale to reduce antibiotics for respiratory tract infections: a controlled before and after study. Fam Pract. 2009;26:183-7.

36. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010;8:124-33.

37. Kazandjian D, Chiew R, Gilbert GL. Rapid diagnosis of Legionella pneumophila serogroup 1 infection with the Binax enzyme immunoassay urinary antigen test. J Clin Microbiol. 1997;35:954-6.

38. Dominguez JA, Gali N, Pedroso P, et al. Comparison of the Binax Legionella urinary antigen enzyme immunoassay (EIA) with the Biotest Legionella Urin antigen EIA for detection of Legionella antigen in both concentrated and nonconcentrated urine samples. J Clin Microbiol. 1998;36:2718-22.

39. Yzerman EP, Den Boer JW, Lettinga KD, Schellekens J, Dankert J, Peeters M. Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in The Netherlands. J Clin Microbiol. 2002;40:3232-6.

40. Wiersinga WJ, Bonten MJ, Boersma WG, et al. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) guidelines on the management of community-acquired pneumonia in adults. Neth J Med. 2012;70:90-101.

41. Andreo F, Dominguez J, Ruiz J, et al. Impact of rapid urine antigen tests to determine the etiology of community-acquired pneumonia in adults. Respir Med. 2006;100:884-91.

42. Diederen BM, Peeters MF. Rapid diagnosis of pneumococcal pneumonia in adults using the Binax NOW Streptococcus pneumoniae urinary antigen test. Int J Infect Dis. 2007;11:284-5.

43. Dominguez J, Gali N, Blanco S, et al. Detection of Streptococcus pneumoniae antigen by a rapid immunochromatographic assay in urine samples. Chest. 2001;119:243-9.

44. Gutierrez F, Masia M, Rodriguez JC, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of Streptococcus pneumoniae urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis. 2003;36(3):286-92.

45. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis. 2010;50:202-9.

46. Murdoch DR, Laing RT, Mills GD, et al. Evaluation of a rapid immunochromatographic test for detection of Streptococcus pneumoniae antigen in urine samples from adults with community-acquired pneumonia. J Clin Microbiol 2001;39:3495-8.

47. Roson B, Fernandez-Sabe N, Carratala J, et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis. 2004;38:222-6.

48. Smith MD, Derrington P, Evans R, et al. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW Streptococcus pneumoniae urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol. 2003;41:2810-3.

49. Sorde R, Falco V, Lowak M, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med. 2011;171:166-72.

50. Boulware DR, Daley CL, Merrifield C, Hopewell PC, Janoff EN. Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. J Infect. 2007;55:300-9.

51. Andreo F, Ruiz-Manzano J, Prat C, et al. Utility of pneumococcal urinary antigen detection in diagnosing exacerbations in COPD patients. Respir Med. 2010;104:397-403.

52. Guchev IA, Yu VL, Sinopalnikov A, Klochkov OI, Kozlov RS, Stratchounski LS. Management of nonsevere pneumonia in military trainees with the urinary antigen test for Streptococcus pneumoniae: an innovative approach to targeted therapy. Clin Infect Dis. 2005;40:1608-16.

53. Stralin K, Holmberg H. Usefulness of the Streptococcus pneumoniae urinary antigen test in the treatment of community-acquired pneumonia. Clin Infect Dis. 2005;41:1209-10.

54. Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000;28:977-83.

55. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet. 2004;363:600-7.

56. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care. Med. 2006;174:84-93.

57. Kristoffersen KB, Sogaard OS, Wejse C, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission--a randomized trial. Clin Microbiol Infect. 2009;15:481-7.

58. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA. 2009;302:1059-66.

59. File TM, Jr., Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. J Antimicrob Chemother. 2007;60:112-20.

60. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother. 2004;54:515-23.

61. el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ. 200610;332:1355.

62. Abdeldaim G, Herrmann B, Molling P, et al. Usefulness of real-time PCR for lytA, ply, and Spn9802 on plasma samples for the diagnosis of pneumococcal pneumonia. Clin Microbiol Infect. 2010;16:1135-41.

63. Carvalho MG, Tondella ML, McCaustland K, et al. Evaluation and improvement of real-time PCR assays targeting lytA, ply, and psaA genes for detection of pneumococcal DNA. J Clin Microbiol. 2007;45:2460-6.

64. Kee C, Palladino S, Kay I, et al. Feasibility of real-time polymerase chain reaction in whole blood to identify Streptococcus pneumoniae in patients with community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;61:72-5.

65. Vernet G, Saha S, Satzke C, et al. Laboratory-based diagnosis of pneumococcal pneumonia: state of the art and unmet needs. Clin Microbiol Infect. 2011;17(Suppl 3):1-13.

66. Johansson N, Kalin M, Giske CG, Hedlund J. Quantitative detection of Streptococcus pneumoniae from sputum samples with real-time quantitative polymerase chain reaction for etiologic diagnosis of community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;60:255-61.

67. Hirama T, Yamaguchi T, Miyazawa H, et al. Prediction of the pathogens that are the cause of pneumonia by the battlefield hypothesis. PLoS One. 2011;6:e24474.

68. Lorente ML, Falguera M, Nogues A, Gonzalez AR, Merino MT, Caballero MR. Diagnosis of pneumococcal pneumonia by polymerase chain reaction (PCR) in whole blood: a prospective clinical study. Thorax. 2000;55:133-7.

69. Smith MD, Sheppard CL, Hogan A, et al. Diagnosis of Streptococcus pneumoniae infections in adults with bacteremia and community-acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection. J Clin Microbiol. 2009;47:1046-9.

70. Peters RP, de Boer RF, Schuurman T, et al. Streptococcus pneumoniae DNA load in blood as a marker of infection in patients with community-acquired pneumonia. J Clin Microbiol. 2009;47:3308-12.

71. Rello J, Lisboa T, Lujan M, et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest. 2009;136:832-40.

72. Kivihya-Ndugga L, van Cleeff M, Juma E, et al. Comparison of PCR with the routine procedure for diagnosis of tuberculosis in a population with high prevalences of tuberculosis and human immunodeficiency virus. J Clin Microbiol. 2004;42:1012-5.

73. Liu FC, Chen PY, Huang F, Tsai CR, Lee CY, Wang LC. Rapid diagnosis of Mycoplasma pneumoniae infection in children by polymerase chain reaction J Microbiol Immunol Infect. 2007;40:507-12.

74. Murdoch DR. Molecular genetic methods in the diagnosis of lower respiratory tract infections. APMIS. 2004;112:713-27.

75. Sotir MJ, Cappozzo DL, Warshauer DM, et al. Evaluation of polymerase chain reaction and culture for diagnosis of pertussis in the control of a county-wide outbreak focused among adolescents and adults. Clin Infect Dis. 2007;44:1216-9.

76. Wegdam-Blans MC, Nabuurs-Franssen MN, Horrevorts AM, Peeters MF, Schneeberger PM, Bijlmer HA. [Laboratory diagnosis of acute Q fever). Ned Tijdschr Geneeskd. 2010;154:A2388.

77. Oosterheert JJ, van Loon AM, Schuurman R, et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. Clin Infect Dis. 2005;41:1438-44.

78. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1-55.

79. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27-S72.

80. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243-50.

81. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-82.

82. Caballero J, Rello J. Combination antibiotic therapy for community-acquired pneumonia. Ann Intensive Care. 2011;1:48.

83. Waterer GW. Monotherapy versus combination antimicrobial therapy for pneumococcal pneumonia. Curr Opin Infect Dis. 2005;18:157-63.

84. Weiss K, Tillotson GS. The controversy of combination vs monotherapy in the treatment of hospitalized community-acquired pneumonia. Chest. 2005;128:940-6.

85. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest. 2003;123:1503-11.

86. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann Pharmacother. 2000;34:446-52.

87. Garcia VE, Mensa J, Martinez JA, et al. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis. 2005;24:190-5.

88. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med. 1999;159:2562-72.

89. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states : 1993, 1995, and 1997. Chest. 2001;119:1420-6.

90. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: Improved outcomes with macrolides but not fluoroquinolones. Chest. 2007;131:466-73.

91. Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N. Impact of intravenous {beta}-lactam/macrolide versus {beta}-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. J Antimicrob Chemother. 2009;63:1025-33.

92. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis. 2003;36:389-95.

93. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978-1997. Am J Med. 1999;107(1A):34S-43S.

94. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med. 2001;161:1837-42.

95. Weiss K, Low DE, Cortes L, et al. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic Streptococcus pneumoniae pneumonia in adults. Can Respir J. 2004;11:589-93.

96. Aspa J, Rajas O, de Rodriguez CF, et al. Impact of initial antibiotic choice on mortality from pneumococcal pneumonia. Eur Respir J. 2006;27:1010-9.

97. Burgess DS, Lewis JS. Effect of macrolides as part of initial empiric therapy on medical outcomes for hospitalized patients with community-acquired pneumonia. Clin Ther. 2000;22:872-8.

98. Dwyer R, Ortqvist A, Aufwerber E, et al. Addition of a macrolide to a ss-lactam in bacteremic pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis. 2006;25:518-21.

99. Ewig S, Hecker H, Suttorp N, Marre R, Welte T. Moxifloxacin monotherapy versus ss-lactam mono- or combination therapy in hospitalized patients with community-acquired pneumonia. J Infect. 2011;62:218-25.

100. Loh LC, Quah SY, Khoo SK, Vijayasingham P, Thayaparan T. Addition of macrolide in treating adult hospitalized community-acquired pneumonia. Respirology. 2005;10:371-7.

101. Paul M, Nielsen AD, Gafter-Gvili A, et al. The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis. Eur Respir J. 2007 Sep;30(3):525-31.

102. Stahl JE, Barza M, DesJardin J, Martin R, Eckman MH. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. Arch Intern Med. 1999;159:2576-80.

103. Kovaleva A, Remmelts HH, Rijkers GT, Hoepelman AI, Biesma DH, Oosterheert JJ. Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. J Antimicrob Chemother. 2012;67:530-40.

104. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ. 1997;315:1151-4.

105. Garnacho-Montero J, Garcia-Cabrera E, Diaz-Martin A, et al. Determinants of outcome in patients with bacteraemic pneumococcal pneumonia: importance of early adequate treatment. Scand J Infect Dis. 2010;42:185-92.

106. Begg N, Cartwright KA, Cohen J, et al. Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. British Infection Society Working Party. J Infect. 1999;39:1-15.

107. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36:296-327.

108. De Pascale G, Bello G, Antonelli M. Steroids in severe pneumonia: a literature review. Minerva Anestesiol. 2011;77:902-10.

109. Salluh JI, Povoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. Crit Care. 2008;12(3):R76.

110. Sibila O, Agusti C, Torres A. Corticosteroids in severe pneumonia. Eur Respir J. 2008;32:259-64.

111. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med. 2005;171:242-8.

112. Fernandez-Serrano S, Dorca J, Garcia-Vidal C, et al. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. Crit Care. 2011;15:R96.

113. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. Chest. 1993;104:389-92.

114. Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377:2023-30.

115. Mikami K, Suzuki M, Kitagawa H, et al. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. Lung. 2007;185:249-55.

116. Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010;181:975-82.

117. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet. 2009;374:1543-56.

118. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. PLoS Med. 2009 May 26;6(5):e1000081.

119. Jansen AG, Rodenburg GD, de Greeff SC, et al. Invasive pneumococcal disease in the Netherlands: Syndromes, outcome and potential vaccine benefits. Vaccine. 2009;27:2394-401.

120. Jansen AG, Rodenburg GD, van der Ende A, et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. Clin Infect Dis. 2009;49:e23-e29.

121. Weinberger DM, Harboe ZB, Sanders EA, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. Clin Infect Dis. 2010;51:692-9.

122. Siber GR, Mäkelä PH. Pneumococcal Vaccines. Washington DC: ASM Press; 2008.

123. Health Council of the Netherlands. Pneumococcal vaccine in elderly adults and risk groups. The Hague: Health Council of the Netherlands; 2003. Report No.: publication no. 2003/10.

124. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009;180:48-58.

125. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008;(1):CD000422.

126. Lucero MG, Dulalia VE, Nillos LT, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev. 2009;(4):CD004977.

127. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. MMWR Morb Mortal Wkly Rep. 2005;54:893-7.

128. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J. 2000;19:187-95.

129. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139-46.

130. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349:1341-8.

131. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010;201:32-41.

132. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006;368:1495-502.

133. Rodenburg GD, de Greeff SC, Jansen AG, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. Emerg Infect Dis. 2010;16:816-23.

134. Dransfield MT, Nahm MH, Han MK, et al. Superior immune response to protein-conjugate versus free pneumococcal polysaccharide vaccine in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180:499-505.

135. Goldblatt D, Southern J, Andrews N, et al. The immunogenicity of 7-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in adults aged 50-80 years. Clin Infect Dis. 2009;49:1318-25.

136. de Roux A, Schmole-Thoma B, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. Clin Infect Dis. 2008;46:1015-23.

137. Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. J Infect Dis. 2003;187:1639-45.

138. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. Clin Rheumatol. 2011;30:1555-61.

139. Smith KJ, Wateska AR, Nowalk MP, Raymund M, Nuorti JP, Zimmerman RK. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA. 2012;307:804-12.

140. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. N Engl J Med. 2010;362:812-22.

141. Hak E, Grobbee DE, Sanders EA, et al. Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. Neth J Med. 2008;66:378-83.

142. Boersma WG, Lowenberg A, Holloway Y, Kuttschrutter H, Snijder JA, Koeter GH. Pneumococcal capsular antigen detection and pneumococcal serology in patients with community acquired pneumonia. Thorax. 1991;46:902-6.

143. Bohte R, van Furth R, van den Broek PJ. Aetiology of community-acquired pneumonia: a prospective study among adults requiring admission to hospital. Thorax. 1995;50:543-7.

144. Braun JJ, de Graaff CS, de Goey J, Zwinderman AH, Petit PL. [Community-acquired pneumonia: pathogens and course in patients admitted to a general hospital). Ned Tijdschr Geneeskd. 2004;148:836-40.

145. van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Jansen HM, Boersma WG. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis. 2005;24:241-9.

146. Steinhoff D, Lode H, Ruckdeschel G, et al. Chlamydia pneumoniae as a cause of community-acquired pneumonia in hospitalized patients in Berlin. Clin Infect Dis. 1996;22:958-64.

147. Garbino J, Sommer R, Gerber A, et al. Prospective epidemiologic survey of patients with community-acquired pneumonia requiring hospitalization in Switzerland. Int J Infect Dis. 2002;6:288-93.

148. Venkatesan P, Gladman J, Macfarlane JT, et al. A hospital study of community acquired pneumonia in the elderly. Thorax. 1990;45:254-8.

149. Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax. 2001;56:296-301.

150. Howard LS, Sillis M, Pasteur MC, Kamath AV, Harrison BD. Microbiological profile of community-acquired pneumonia in adults over the last 20 years. J Infect. 2005;50:107-13.

151. Levy M, Dromer F, Brion N, Leturdu F, Carbon C. Community-acquired pneumonia. Importance of initial noninvasive bacteriologic and radiographic investigations. Chest. 1988;93:43-8.

152. Ausina V, Coll P, Sambeat M, et al. Prospective study on the etiology of community-acquired pneumonia in children and adults in Spain. Eur J Clin Microbiol Infect Dis. 1988;7:342-7.

153. Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community-acquired pneumonia. Etiology, prognosis, and treatment. Am Rev Respir Dis. 1990;142:369-73.

154. Blanquer J, Blanquer R, Borras R, et al. Aetiology of community acquired pneumonia in Valencia, Spain: a multicentre prospective study. Thorax. 1991;46:508-11.

155. Almirall J, Boixeda R, Bolibar I, Bassa J, Sauca G, Vidal J, et al. Differences in the etiology of community-acquired pneumonia according to site of care: a population-based study. Respir Med. 2007;101:2168-75.

156. Pareja A, Bernal C, Leyva A, Piedrola G, Maroto MC. Etiologic study of patients with community-acquired pneumonia. Chest. 1992;101:1207-10.

157. Falco V, Fernandez de ST, Alegre J, Ferrer A, Martinez Vazquez JM. Legionella pneumophila. A cause of severe community-acquired pneumonia. Chest. 1991;100:1007-11.

158. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M. Is Streptococcus pneumoniae the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med. 1999;106:385-90.

159. Sopena N, Sabria M, Pedro-Botet ML, et al. Prospective study of community-acquired pneumonia of bacterial etiology in adults. Eur J Clin Microbiol Infect Dis. 1999;18:852-8.

160. Fernandez-Sabe N, Carratala J, Roson B, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. Medicine (Baltimore). 2003;82:159-69.

161. Menendez R, Cordoba J, de la Cuadra P, et al. Value of the polymerase chain reaction assay in noninvasive respiratory samples for diagnosis of community-acquired pneumonia. Am J Respir Crit Care Med. 1999;159:1868-73.

162. Ruiz M, Ewig S, Marcos MA, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med. 1999;160:397-405.

163. Cilloniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax. 2011;66:340-6.

164. Zalacain R, Torres A, Celis R, et al. Community-acquired pneumonia in the elderly: Spanish multicentre study. Eur Respir J. 2003;21:294-302.

165. Falguera M, Sacristan O, Nogues A, et al. Nonsevere community-acquired pneumonia: correlation between cause and severity or comorbidity. Arch Intern Med. 2001;161:1866-72.

166. Marcos MA, Jimenez de Anta MT, de la Bellacasa JP, et al. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. Eur Respir J. 2003;21:209-14.

167. Briones ML, Blanquer J, Ferrando D, Blasco ML, Gimeno C, Marin J. Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults. Clin Vaccine Immunol. 2006;13:1092-7.

168. Angeles MM, Camps M, Pumarola T, et al. The role of viruses in the aetiology of community-acquired pneumonia in adults. Antivir Ther. 2006;11:351-9.

169. Socan M, Marinic-Fiser N, Kraigher A, Kotnik A, Logar M. Microbial aetiology of community-acquired pneumonia in hospitalised patients. Eur J Clin Microbiol Infect Dis. 1999;18:777-82.

170. Beovic B, Bonac B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. Eur J Clin Microbiol Infect Dis. 2003;22:584-91.

171. Kerttula Y, Leinonen M, Koskela M, Makela PH. The aetiology of pneumonia. Application of bacterial serology and basic laboratory methods. J Infect. 1987;14:21-30.

172. Holmberg H. Aetiology of community-acquired pneumonia in hospital treated patients. Scand J Infect Dis. 1987;19:491-501.

173. Burman LA, Trollfors B, Andersson B, et al. Diagnosis of pneumonia by cultures, bacterial and viral antigen detection tests, and serology with special reference to antibodies against pneumococcal antigens. J Infect Dis. 1991;163:1087-93.

174. Ostergaard L, Andersen PL. Etiology of community-acquired pneumonia. Evaluation by transtracheal aspiration, blood culture, or serology. Chest. 1993;104:1400-7.

175. Stralin K, Olcen P, Tornqvist E, Holmberg H. Definite, probable, and possible bacterial aetiologies of community-acquired pneumonia at different CRB-65 scores. Scand J Infect Dis. 2010;42:426-34.

176. Hohenthal U, Vainionpaa R, Meurman O, et al. Aetiological diagnosis of community acquired pneumonia: utility of rapid microbiological methods with respect to disease severity. Scand J Infect Dis. 2008;40:131-8.

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REVIEW

Sarcoidosis of the liver: to treat or not to treat?

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ABSTRACT

Introduction: Sarcoidosis is a non-caseating, granulomatous disease of incompletely understood aetiology that can affect nearly all organs including the liver. Hepatic involvement is thought to occur in 50-90% of patients but may remain undiagnosed in many cases. Evidence-based guidelines for the treatment of sarcoidosis of the liver are lacking. Patients usually receive no treatment or are treated pragmatically with corticosteroids. However, treatment with systemic corticosteroids has had mixed results. The use of ursodeoxycholic acid (UDCA) in the treatment of sarcoidosis-associated cholestasis has been reported by several groups, and is empirically prescribed to sarcoidosis patients with hepatic involvement.

Methods: The effect of UDCA on symptoms and serum liver tests was investigated in a retrospective cohort study in which hepatic sarcoidosis patients had received either no treatment, prednisolone treatment or UDCA treatment. For all patients, laboratory results on ASAT, ALAT, AP and GGT were collected. Patients described the severity of their symptoms before and after treatment on a numerical scale.

Results: A total of 17 patients participated in the study. Serum liver tests in the group treated with UDCA had improved as compared with the other groups. Also, symptomatic improvement of pruritus and fatigue was reported in the group treated with UDCA.

Conclusion: This retrospective cohort study supports the empirical first-line use of UDCA in the treatment of sarcoidosis of the liver, especially in symptomatic patients. Prospective randomised trials are needed to adequately support this concept.

KEYWORDS

Sarcoidosis, liver, cholestasis, ursodeoxycholic acid

INTRODUCTION

Sarcoidosis is a systemic non-caseating granulomatous disease of as yet enigmatic aetiology which can affect nearly every organ.[1] Sarcoidosis is diagnosed at all ages but incidence peaks between 20 and 40 years.[2] Women are more often affected than men.[2-7] The prevalence in the United States was reported in a wide range between 1 and 40 per 100,000.[8] Its exact prevalence in the Netherlands is unknown, but is expected to be in the same order of magnitude. Although sarcoidosis is described in all ethnicities,[2,3] its prevalence in African descendents is at least two to threefold higher than in Caucasians.[2,6,7,9,10] Remarkably, disease severity also differs between ethnicities with involvement of skin, liver, eye and bone marrow more frequently observed in patients of African origin than in Caucasians.[2-6] The lungs are affected in up to 90% of patients.[11,12]

Liver involvement in patients with sarcoidosis ranges from 50 to 90%,[4,9,13] but may go unnoticed in case of mild serum liver test abnormalities in the absence of liver-related symptoms. Conversely, elevated serum liver tests and symptoms related to hepatic involvement may be among the earliest manifestations of this systemic disease.[4] Clinical symptoms of liver involvement include fatigue, pruritus and right upper quadrant abdominal pain in 15%[9] and jaundice, weight loss and fever in 5% of patients.[4,9] Serum liver tests usually reveal a cholestatic pattern with elevation of serum alkaline phosphatase (AP) in up to 90% and often only mildly elevated serum transaminases in 50-70%.[4,14-16] Decompensated liver disease with portal hypertension and development of varices, variceal bleeding, ascites, or hepatic encephalopathy are late complications of hepatic sarcoidosis. The risk factors for development of end-stage liver disease due to sarcoidosis of the liver are unclear, as is the exact percentage of patients who reach this stage after a chronic course of disease.

Evidence-based guidelines for treatment of sarcoidosis of the liver do not exist. Most patients remain untreated. Corticosteroids, which represent the standard treatment of advanced pulmonary, cerebral or ocular sarcoidosis, were administered in case series. However, treatment with systemic corticosteroids has had mixed results.[13,17] Apparently, corticosteroids do not prevent development of portal hypertension.[4,17,18] Thus, systemic corticosteroids have been recommended only when organ function is imminently threatened.[13] The effects of targeted anti-TNF-alpha therapy, which in one randomised study has shown to be marginally effective in sarcoidosis of the lung when disease activity prohibited the tapering of corticosteroids,[19] has not been evaluated for the hepatic manifestation.

Ursodeoxycholic acid (UDCA) has well-known anticholestatic and hepatoprotective properties[20] and is the evidence-based standard treatment of cholestatic disorders such as primary biliary cirrhosis[21] and intrahepatic cholestasis of pregnancy,[22] but is also applied in a number of other orphan chronic progressive cholestatic disorders for which no long-term therapeutic trials of adequate size and dose exist.[23] Although randomised controlled trials have not been performed in sarcoidosis of the liver, UDCA has been widely used.[14,24,25] This practice is supported by the favourable safety profile of UDCA,[14] and its efficacy in improving serum liver tests in hepatic sarcoidosis[14,24,25] but not by improvement of validated surrogate markers of long-term prognosis.

In order to gain more insight into treatment response and pathogenesis of hepatic sarcoidosis, including the use of UDCA in these patients, we retrospectively investigated a group of 25 patients diagnosed with liver sarcoidosis in a tertiary care centre in the Netherlands (the Academic Medical Centre (AMC) in Amsterdam). Patients were interviewed and serum liver tests were analysed to determine subjective and biochemical effects of different treatment options. Patients had received either no treatment or treatment with prednisolone or UDCA.

METHODS

Design

In this retrospective cohort study, we investigated the effect of UDCA on symptoms and serum liver tests. A list of all patients known to be followed with sarcoidosis of the liver in the hepatology outpatient clinic of the AMC in Amsterdam, the Netherlands (a tertiary hospital) in the past five years was used to select patients for inclusion in this study. The following inclusion criteria were applied: patients diagnosed with sarcoidosis of the liver, regardless of this being classical liver disease in which the disease is only manifest in the liver, or generalised disease, who were alive at the time of inclusion (1 January 2010). Patients whose aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (AP) and gamma glutamyltransferase (GGT) values were not available for all time points outlined below were excluded from the biochemical response to treatment analysis.

Effect of treatment on clinical symptoms

To obtain information about the effects of treatment on liver-related symptoms, all patients were approached for active participation in this study. Those patients who provided informed consent were invited in person to the outpatient clinic to answer a series of questions on their demography and life history as well as on the course of their clinical symptoms. They were asked to retrospectively score their fatigue and itch as subjective measures of the efficacy of treatment, grading these symptoms on a scale ranging from 0 to 10 (0 being no fatigue or no itch, respectively; 10 being the worst imaginable fatigue or itch, respectively).

As the study only included face-to-face interviews and no medical interventions, the local medical ethics committee waived the necessity of a full medical ethical evaluation. Data were analysed using GraphPad Prism version 5.01. For statistic analyses paired t-tests were performed to evaluate the significance of changes over time within the treatment groups.

Biochemical response to treatment

In a second part of the study we retrospectively collected data on liver biochemistry before and after treatment. Demographic data, date of diagnosis, applied treatment and date of start of treatment were obtained from the medical files of the selected patients. Patients were grouped as having received either no treatment, prednisolone treatment or UDCA treatment. For all patients, serum liver tests (ASAT, ALAT, AP and GGT) before start of treatment, at start of treatment (t = 0) and at three months after start of treatment (t = +3 months) were collected. The time points used to determine biochemistry before start of treatment depended on the available laboratory data. The difference between start of treatment and available data from before start of treatment ranged from 3 to 188 days (median 49 days). For the group that received no treatment, the date of the first available laboratory investigation after onset of symptoms was used as the first time point.

Statistical evaluation

Data are given as mean ± SD or median. Clinical and biochemical results at start of treatment and after three months were analysed with a paired t-test. $P<0.05$ was considered significant.

RESULTS

Study cohort

A total of 25 patients diagnosed with sarcoidosis of the liver were identified and approached by a patient information letter with background information to participate in the study. Contact was established with 20 patients, 17 of whom agreed to participate. These patients were invited to the hepatology outpatient clinic and asked to report their liver-related symptoms before treatment and after three months of treatment. One patient did not show up at the interview. Of the initial 25 patients, 17 met the criteria for inclusion in the biochemical analysis (*figure 1*).

Of the 16 interviewed patients, their country of birth was: Suriname (n=10), the Netherlands (n=2), Ghana (n=2), Curacao (n=1) and Morocco (n=1). The ethnic affiliation of 23 of 25 patients could be traced, Creole (n=13), Hindustani (n=4), Caucasian and Ghanaian (n=2 each) and Arabic (n=1). Concerning direct heredity of the disease we found that two patients had one second-degree relative diagnosed with sarcoidosis, and one patient had one first-degree and four second-degree relatives diagnosed with sarcoidosis. Questions regarding allergies/hypersensitivities and the exposure to potentially harmful substances did not yield any new insights. In nine patients the sarcoidosis was only manifest in the liver. A total of seven patients had extrahepatic manifestations of sarcoidosis. Reported comorbidities included: arterial hypertension (n=6), diabetes type 2 (n=5; 2 prednisolone-induced), sickle cell anaemia (n=1), and HIV positivity (n=1). In one patient a liver transplantation was performed during the course of the disease.

Reported liver-related symptoms and change during treatment

A total of ten patients reported liver-related symptoms. The most common liver-related symptoms were fatigue (n=9) and itch (n=8). Patients were asked to rate their fatigue and itch before and three months after treatment was initiated on a visual analogue scale from 0 to 10 (0 = lowest, 10 = highest). *Figure 2* shows the effect of no treatment, prednisolone and UDCA treatment on fatigue, and *figure 3*

Figure 2. *Evaluation of fatigue symptoms scored on an intensity scale and change after three months of therapy (intensity of 0 representing no symptoms and 10 representing the maximum imaginable intensity of the symptom). Only patients treated with UDCA reported a significant reduction of fatigue three months after start of treatment. * p<0.05 (paired t-test)*

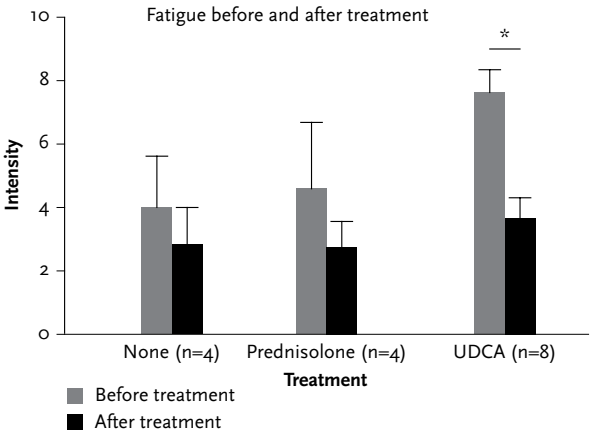


Figure 1. *Flowchart of the study*

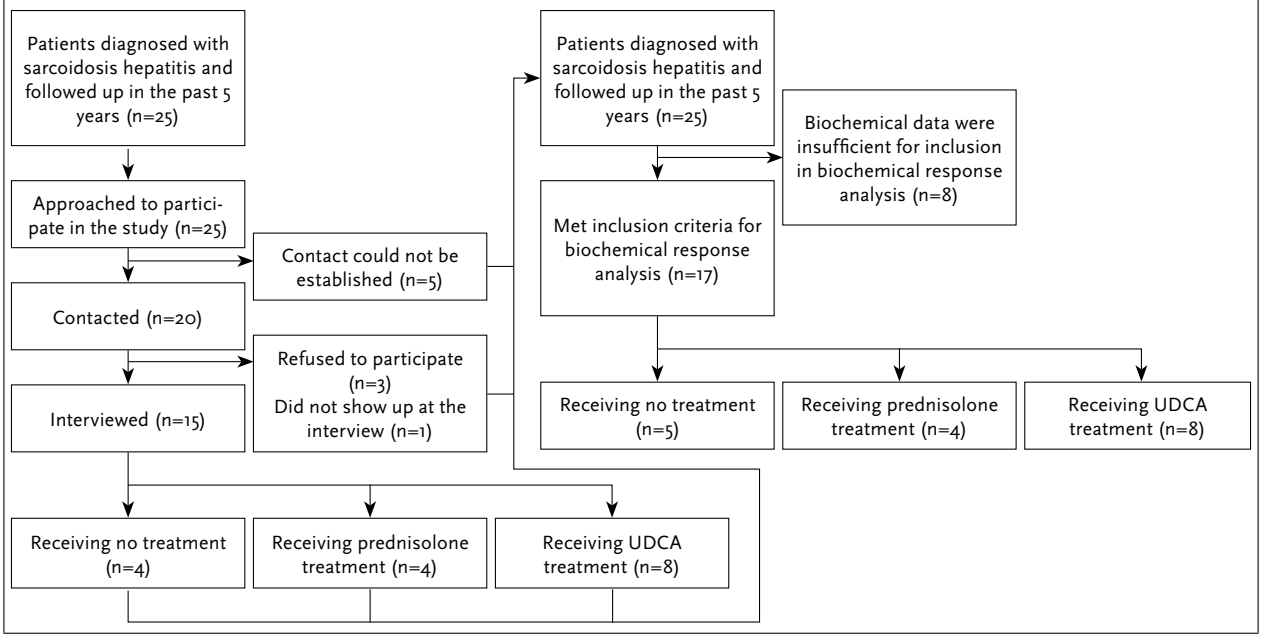
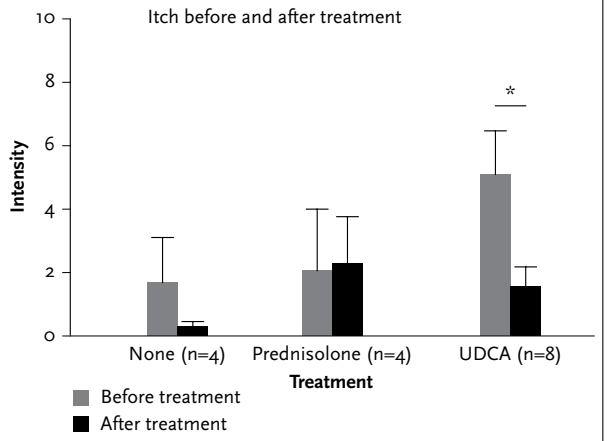


Figure 3. *Evaluation of fatigue symptoms scored on an intensity scale and change after three months of therapy (intensity of 0 representing no symptoms and 10 representing the maximum imaginable intensity of the symptom). Only patients treated with UDCA reported a significant reduction of itch three months after start of treatment. * p<0.05, paired t-test*



shows the effect of treatment on itch. The average ratings of fatigue of patients treated with prednisolone changed from 4.1/10 to 2.8/10 (p=0.51), and the ratings of itch changed from 2.0/10 to 2.3/10 (significance of change within treatment group p=0.82). The average ratings of itch of patients treated with UDCA changed from 5.0/10 to 1.5/10 after treatment (p<0.05). The patients receiving no treatment were asked to rate their fatigue and itch at the time of diagnosis and at the time of the interview (p=0.39). Of the eight patients who received UCDA, the only reported side effect was short-term diarrhoea (reported by two patients, not leading to treatment discontinuation).

Patients included in the biochemical response analysis

Seventeen patients met the criteria for inclusion in the biochemical response analysis (*figure 1*). Based on the medication history documented in the medical files and the electronic medication information system, patients were grouped as those who did not receive treatment (n=5), those who received prednisolone treatment (n=3, initial dose up to 30 mg/day before tapering down), and those who received UDCA treatment (n=9, doses of 10-15 mg/kg/day). Patient characteristics are summarised in *table 1*. *Table 2* shows the baseline serum values of ALAT, ASAT, AP and GGT of the patients.

Biochemical response to treatment

The biochemical response to prednisolone and UDCA treatment in patients with sarcoidosis of the liver was compared with the course of biochemical tests of patients that did not receive any treatment (*figures 4* and *5*).

Table 1. *Characteristics of 17 patients with sarcoidosis of the liver included in the biochemical response analysis*

	Total (n=17)	No treatment (n=5)	Prednisolone (n=3)	UDCA (n=9)
Median age, years (range)	50 (37-77)	46 (42-77)	61 (51-75)	48 (37-59)
Sex (%)				
- Male	10 (59%)	2 (40%)	3 (100%)	5 (56%)
- Female	7 (41%)	3 (60%)	0 (0%)	4 (44%)

Table 2. *Serum liver tests at start of treatment (t=0) of patients included in the biochemical response analysis*

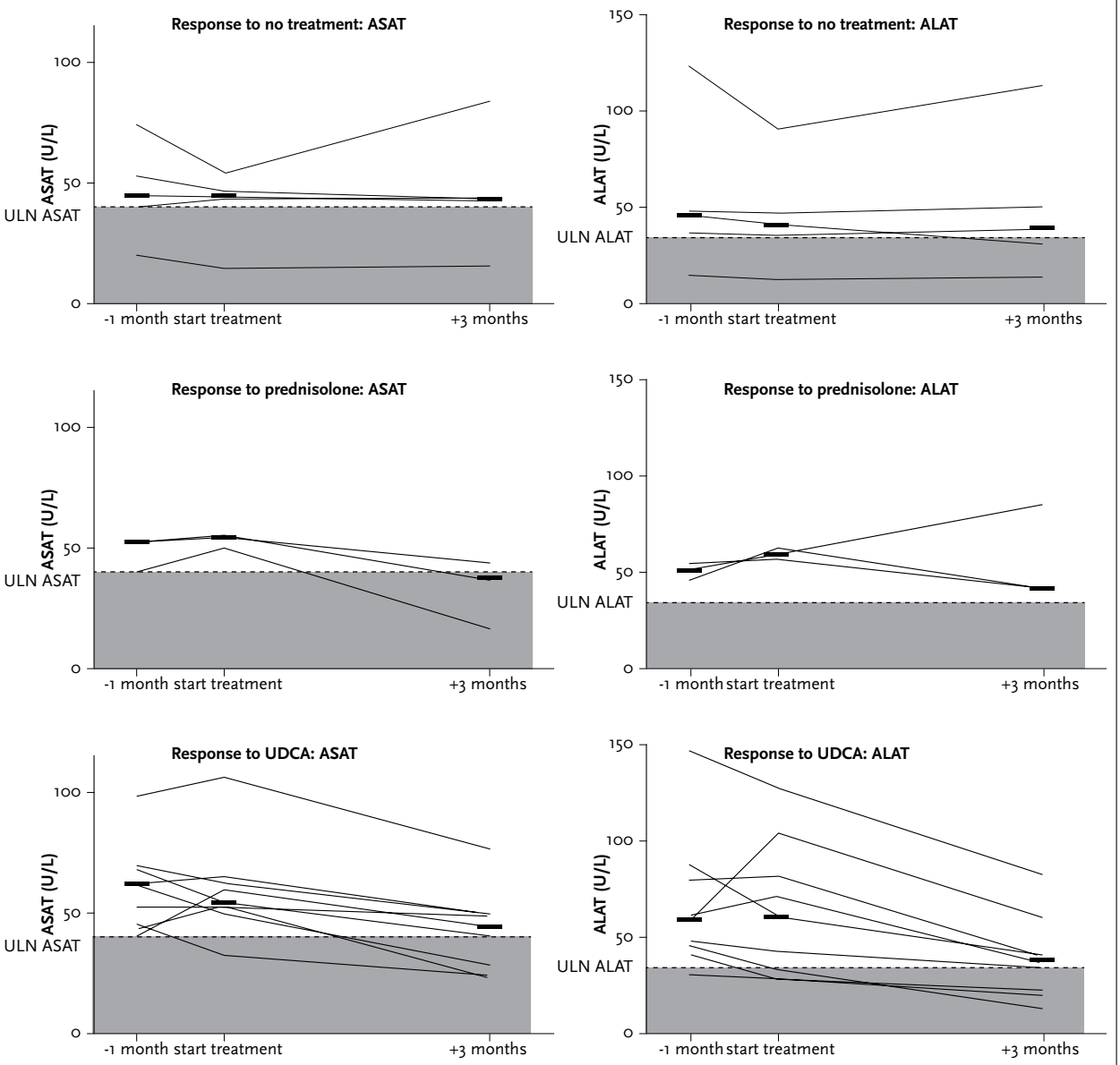
	Total (n=17)	No treatment (n=5)	Prednisolone (n=3)	UDCA (n=9)
ASAT [IU/l], median (range)	54 (15-107)	44 (15-54)	55 (50-56)	55 (33-107)
ALAT [IU/l], median (range)	57 (12-128)	41 (12-90)	60 (57-63)	62 (29-128)
AP [IU/l], median (range)	325 (58-1161)	176 (58-438)	549 (198-1161)	363 (109-625)
GGT [IU/l], median (range)	340 (23-1544)	342 (23-644)	337 (317-1544)	337 (112-1119)

As compared with the values on day 1 of treatment (t = 0), we found a mean change of ASAT, ALAT, AP and GGT after three months of -40.0%±23.6%, -6.5%±42.0%, -54.0%±41.3% and -15.2%±60.9%, respectively, in the group treated with prednisolone, of -28.1%±13.1%, -37.2%±14.2%, -30.8%±27.4% and -41.1%±40.9%, respectively, in the group treated with UDCA; and a mean change of +10.7%±25.6%, +6.9%±18.9%, -2.4%±9.0% and +4.4%±17.1%, respectively, in the group that did not receive any treatment aimed at the liver sarcoidosis. Within the treatment groups ASAT, ALAT, AP and GGT at t = 3 months as compared with t = 0 did not differ significantly for the no treatment and prednisolone groups, while serum liver tests were significantly lower in the UDCA group after three months of treatment (p<0.05 for ASAT, ALAT, AP, GGT, paired t-tests).

DISCUSSION

Sarcoidosis of the liver is a barely studied and probably under-diagnosed manifestation of sarcoidosis. It may progress to cirrhosis and subsequent complications of portal hypertension. Patients often receive no treatment, or are pragmatically treated with corticosteroids. The present retrospective study compared the effects of prednisolone to those of the anticholestatic bile acid ursodeoxycholic acid (UDCA). The results suggest that UDCA improves

Figure 4. *Biochemical response to treatment: ASAT and ALAT. Values for ASAT and ALAT are shown for all individual patients (thin lines), and median values are shown (thick horizontal bars) for t = -1 month, t = 0 and t = +3 months. ULN = upper limit of normal*

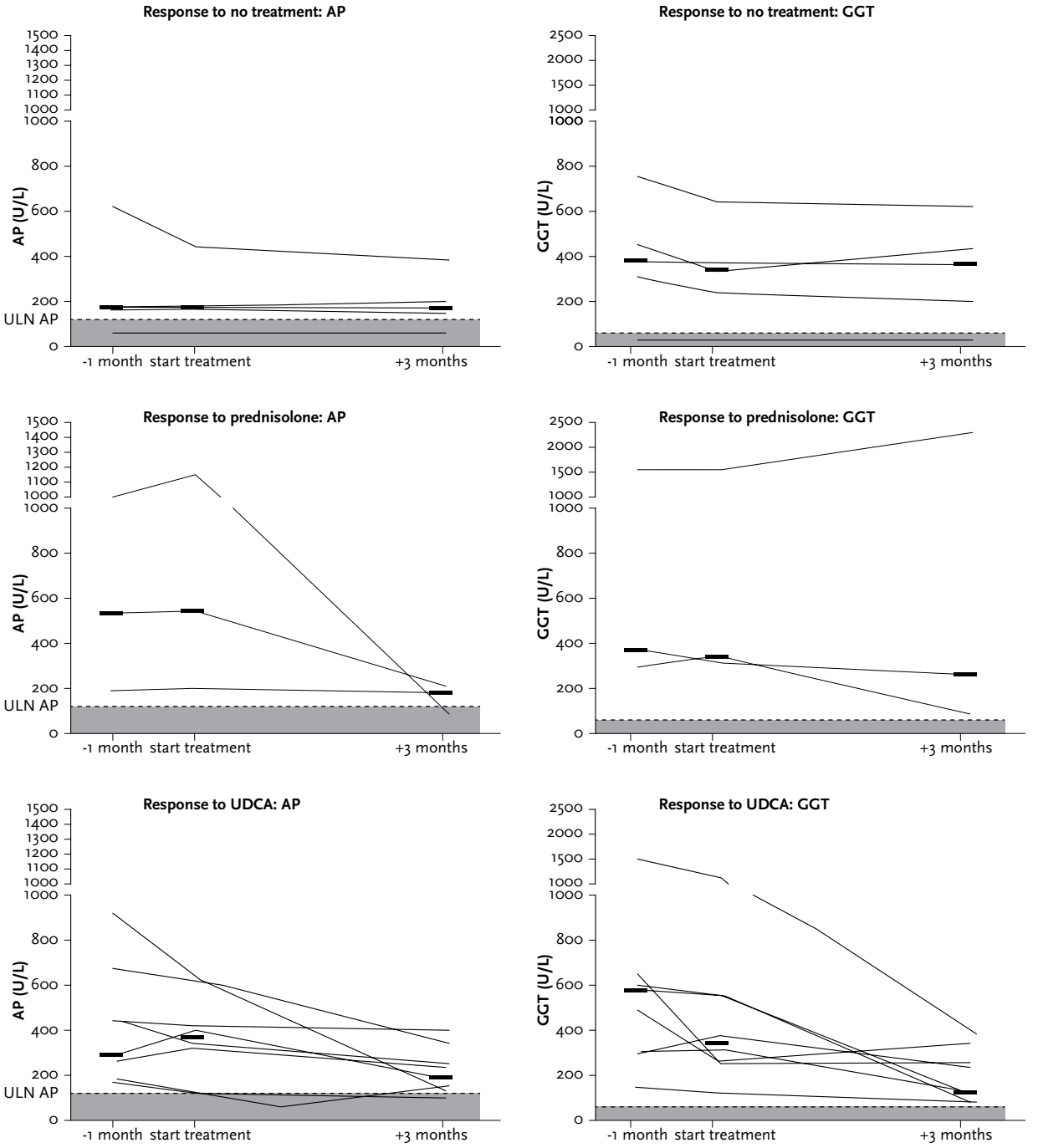


not only serum liver tests, but also clinical symptoms of fatigue and pruritus in patients with sarcoidosis of the liver. The short-term effect of UDCA was superior to that of prednisolone in the cohort under study.

The effect of corticosteroids on sarcoidosis of the liver has never been assessed in properly controlled trials.[26] Corticosteroids may be ineffective in improving serum liver tests as surrogate markers of cholestasis and tissue inflammation, and do not seem to prevent portal hypertension.[4,17,18]

The rationale to use UDCA as a first-line drug and potential alternative to corticosteroid treatment in liver sarcoidosis is based on its beneficial effect in other chronic cholestatic liver diseases. UDCA is today regarded as standard treatment of primary biliary cirrhosis (PBC), a florid, destructive, non-purulent, granulomatous cholangitis.[23] In PBC, UDCA markedly improves serum liver tests and histological inflammatory activity, delays development of fibrosis, cirrhosis and complications of portal hypertension and normalises life expectancy in two

Figure 5. *Biochemical response to treatment or no treatment: AP and GGT. Values are shown for all individual patients (thin lines). Median values (thick horizontal bars) are shown for t = -1 month, t = 0 and t = +3 months. ULN = upper limit of normal*



of three treated patients.[23] UDCA is also regarded as the first-line treatment of intrahepatic cholestasis of pregnancy (ICP) where it improves serum liver tests in the mother, effectively reduces pruritus and may prolong time to often premature delivery in ICP towards normal.[22,23] UDCA is a well-characterised drug with an exceptionally mild side effect profile[27] when applied at therapeutic doses of 13-15(-20) mg/kg daily.

Mechanisms and sites of action of UDCA in cholestatic liver diseases have increasingly been unravelled.[27] UDCA acts as a posttranscriptional secretagogue both in hepatocytes and cholangiocytes and, thereby, stimulates

impaired hepatobiliary secretion.[27] In addition, UDCA has antiapoptotic properties and decreases bile cytotoxicity by reducing the levels of endogenous, potentially toxic hydrophobic bile acids.[28-30]

Our retrospective cohort study in a tertiary care centre provides support to the practice of treating symptomatic sarcoidosis of the liver with UDCA. Although the available literature shows no reduction of lesions in liver biopsies after treatment with either corticosteroids or UDCA,[14,24,31] both treatment options seem to have a positive effect on liver biochemistry. Patients in our study group who received no treatment showed no significant changes in liver enzyme levels. These findings are in line with earlier case reports of patients with sarcoidosis of the liver who were successfully treated with UDCA.[14,24,25]

The subjective effects of treatment are an important measure of drug efficacy. In this study we addressed this issue by asking patients to retrospectively score their fatigue and pruritus on a scale from 0 to 10 before treatment and at the moment of the interview. We found a consistent decrease of pruritus in the group treated with UDCA. Furthermore, subjective measures of fatigue had improved in both the group treated with corticosteroids and the group treated with UDCA. With the only reported side effect being transient diarrhoea in two out of eight patients treated with UDCA, this therapy appeared generally well tolerated.

The prevalence of sarcoidosis of the liver is at least two to threefold higher in African Americans than in Caucasians.[2,6,7,9] This is supported by our findings, as the majority of our cohort has a Creole ethnicity (16/25). We did not find any conclusive explanation in the literature for this overrepresentation of individuals whose genealogy can at least in part be tracked back to forbears originating from the many peoples of Africa.

Our study has several important limitations. First of all, as sarcoidosis of the liver is a rare disease and as this was a single-centre study, we had to resort to a retrospective study design, and still our number of patients was limited. As the data were collected in a retrospective, cross-sectional manner several possibilities for bias exist. The interviews with patients were conducted at different time points during the follow-up of their disease, and patient answers may therefore be less reliable. Furthermore, as no standardised and validated questionnaires exist for the evaluation of liver sarcoidosis symptoms we relied on a self-composed questionnaire which has not been tested in other studies.
The collection of biochemical data is another possible source of bias. We collected data from the laboratory database using the start date of therapy which was noted in the patient file or in the electronic patient record, and took the blood tests which most closely followed on a calculated date three months after this start date for our analysis of the biochemical response to therapy. In a possible follow-up study data acquisition should be performed in a prospective manner.
Another weakness of the study design is that it was not a prospective study and patients were not randomised to different treatment arms. To our knowledge no randomised controlled clinical trials evaluating the efficacy of different treatment modalities on biochemical and clinical parameters have ever been performed in patients with liver sarcoidosis and although it is understood that there will be substantial difficulties to obtain sufficient patient numbers, funding and organisational support it would be laudable if such a study could be initiated.
Despite the methodological shortcomings of this study, we feel that this rare patient group deserves a higher level of attention, both focusing on the aetiology of the disease and on the optimal therapeutic strategy for these individuals. In our data we see a definite indication that UDCA rather than prednisolone should be evaluated as a first-line drug for the treatment of non-cirrhotic patients with sarcoidosis of the liver.

CONCLUSION

Our retrospective cohort study in a tertiary care centre supports the empirical use of UDCA in the treatment of sarcoidosis of the liver, especially in patients suffering from pruritus. Probably due to its ability to improve impaired biliary secretion and bile flow, its effects in modulating the bile acid composition towards a more hydrophilic and less toxic bile acid pool and its anti-inflammatory effects, UDCA may aid to reduce cholestasis and hepatic and biliary inflammation. Given the very favourable side effect profile at therapeutic daily doses of 13-15(-20) mg/kg and relative low costs of treatment, there seem to be few objections to the pragmatic treatment of hepatic sarcoidosis with UDCA. Based on the published experience with UDCA, both in sarcoidosis and in other cholestatic disorders, we think that patients with hepatic sarcoidosis should be offered UDCA as a first line of treatment, especially in cases with predominant pruritic complaints, as long as no prospective randomised controlled trials are available.

CONFLICTS OF INTEREST

Dr. Beuers has received lecture fees from Falk Foundation, Gilead, Roche and Zambon. He received research support

for 2011 from Zambon. He signed a consultant agreement with Intercept (obeticholic acid). The other authors have no conflicts of interest to declare.

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REFERENCES

1. Wirnsberger RM, de Vries J, Wouters EF, Drent M. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. Neth J Med. 1998;53:53-60.
2. Rybicki BA, Major M, Popovich J, Jr., Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 19971;145:234-41.
3. Pietinalho A, Hiraga Y, Hosoda Y, Lofroos AB, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan. A comparative epidemiological study. Sarcoidosis. 1995;12:61-7.
4. Maddrey WC, Johns CJ, Boitnott JK, Iber FL. Sarcoidosis and chronic hepatic disease: a clinical and pathologic study of 20 patients. Medicine (Baltimore). 1970;49:375-95.
5. Nagai S, Izumi T. Pulmonary sarcoidosis: population differences and pathophysiology. South Med J. 1995;88:1001-10.
6. Gideon NM, Mannino DM. Sarcoidosis mortality in the United States 1979-1991: an analysis of multiple-cause mortality data. Am J Med. 1996100:423-7.
7. Rybicki BA, Iannuzzi MC. Epidemiology of sarcoidosis: recent advances and future prospects. Semin Respir Crit Care Med. 2007;28:22-35.
8. Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester, Minnesota: a population-based study of incidence and survival. Am J Epidemiol. 1986;123:840-5.
9. Devaney K, Goodman ZD, Epstein MS, Zimmerman HJ, Ishak KG. Hepatic sarcoidosis. Clinicopathologic features in 100 patients. Am J Surg Pathol. 1993;17:1272-80.
10. Caldwell SH, Harris DM, Patrie JT, Hespenheide EE. Is NASH underdiagnosed among African Americans? Am J Gastroenterol. 2002;97:1496-500.
11. Lynch JP, 3rd, Sharma OP, Baughman RP. Extrapulmonary sarcoidosis. Semin Respir Infect. 1998;13:229-54.
12. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1885-9.
13. Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. Am J Gastroenterol. 2008;103:3184-92; quiz 93.
14. Alenezi B, Lamoureux E, Alpert L, Szilagyi A. Effect of ursodeoxycholic acid on granulomatous liver disease due to sarcoidosis. Dig Dis Sci. 2005;50:196-200.
15. Israel HL, Margolis ML, Rose LJ. Hepatic granulomatosis and sarcoidosis. Further observations. Dig Dis Sci. 1984;29:353-6.
16. Baughman RP. Sarcoidosis. Usual and unusual manifestations. Chest. 1988;94:165-70.
17. Blich M, Edoute Y. Clinical manifestations of sarcoid liver disease. J Gastroenterol Hepatol. 2004;19:732-7.
18. Valla D, Pessegueiro-Miranda H, Degott C, Lebrec D, Rueff B, Benhamou JP. Hepatic sarcoidosis with portal hypertension. A report of seven cases with a review of the literature. Q J Med. 1987;63:531-44.
19. Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006;174:795-802.
20. de Caestecker JS, Jazrawi RP, Petroni ML, Northfield TC. Ursodeoxycholic acid in chronic liver disease. Gut. 1991;32:1061-5.
21. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med. 2005;353:1261-73.
22. Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology. 2005;129:894-901.
23. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51:237-67.
24. Becheur H, Dall'osto H, Chatellier G, et al. Effect of ursodeoxycholic acid on chronic intrahepatic cholestasis due to sarcoidosis. Dig Dis Sci. 1997;42:789-91.
25. Baratta L, Cascino A, Delfino M, et al. Ursodeoxycholic acid treatment in abdominal sarcoidosis. Dig Dis Sci. 2000;45:1559-62.
26. Vatti R, Sharma OP. Course of asymptomatic liver involvement in sarcoidosis: role of therapy in selected cases. Sarcoidosis Vasc Diffuse Lung Dis. 1997;14:73-6.
27. Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006;3:318-28.
28. Poupon RE, Chretien Y, Poupon R, Paumgartner G. Serum bile acids in primary biliary cirrhosis: effect of ursodeoxycholic acid therapy. Hepatology. 1993;17:599-604.
29. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. Hepatology. 2002;36:525-31.
30. Dilger K, Hohenester S, Winkler-Budenhofer U, et al Effect of ursodeoxycholic acid on bile acid profiles and intestinal detoxification machinery in primary biliary cirrhosis and health. J Hepatol. 2012;57:133-40.
31. Nores JM, Chesneau MC, Charlier JP, de Saint-Louvent P, Nenna AD. [A case of hepatic sarcoidosis. Review of the literature]. Ann Gastroenterol Hepatol (Paris). 1987;23:257-60.

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REVIEW

Which long-acting bronchodilator is most cost-effective for the treatment of COPD?

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ABSTRACT

Background: The aim of this study was to estimate the cost-effectiveness of tiotropium versus salmeterol to inform decision making within the Dutch healthcare setting.

Methods: A previously published, validated COPD progression model was updated with new exacerbation data and adapted to the Dutch setting by including Dutch estimates of healthcare use for COPD maintenance treatment and Dutch unit costs. Exacerbation data from the POET-COPD trial were combined with evidence from earlier tiotropium studies using Bayesian meta-analysis. The model-based analysis was performed using a one- and five-year time horizon. Main health outcomes were the number of exacerbations and quality-adjusted life years (QALYs).

Results: One-year costs per patient from the healthcare perspective were €1370 for tiotropium and €1359 for salmeterol; a difference of €11 (95% uncertainty interval (UI): -198-212). The annual number of exacerbations was 0.068 (-0.005-0.140) lower in the tiotropium group. The number of QALYs in the tiotropium group was 0.011 (-0.019-0.049) higher, resulting in an incremental cost-effectiveness ratio (ICER) of €1015 per QALY. After five years, the difference in exacerbations, QALYs and costs between the tiotropium and salmeterol group were -0.435 (-0.915-0.107), 0.079 (-0.272-0.520) and €-277 (-1586-1074), respectively, indicating that tiotropium was more effective and less costly. Using a societal perspective, tiotropium dominated salmeterol both after one and five years.

Conclusion: Tiotropium reduced exacerbations and exacerbation-related costs. After one year the cost per QALY of tiotropium compared with salmeterol was very low, while after five years tiotropium was found to dominate salmeterol.

KEYWORDS

Costs, exacerbations, model, quality-adjusted life years, salmeterol, tiotropium

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and treatable disease characterised by persistent airflow limitation that is usually progressive and is accompanied by extrapulmonary effects that can lead to important comorbidities. In the Netherlands the prevalence of COPD is estimated to be as high as 4.1-5.4% for the population above 40 years[1-3] making COPD one of the leading causes of disability and mortality.[4,5] The burden of COPD is substantial and expected to increase in the near future due to ageing of the population and an increase in the prevalence of smoking among women in the past decades. Given the limited healthcare budgets, the need for information on efficient treatment options for COPD in terms of both effects and costs is high. Data on costs and cost-effectiveness are very relevant for guideline development and policy making, because they allow calculating the total costs of using one treatment instead of another treatment and the total effect in return for incurring these costs.

An important part of the treatment of COPD consists of pharmacotherapy to relieve symptoms, improve quality of life and prevent exacerbations. Current national and international guidelines for the treatment of COPD recommend the use of long-acting bronchodilating agents for patients with moderate to very severe COPD (according to the GOLD guidelines).[6-8] Available long-acting bronchodilating agents can be divided into long-acting

beta-agonists (salmeterol, formoterol and indacaterol) and long-acting anticholinergic drugs (tiotropium).[9] Although the Dutch General Practitioners (NHG) guideline for COPD[7] expresses a slight preference for tiotropium in patients with more severe COPD or cardiac comorbidity, other guidelines do not favour one type of long-acting bronchodilator over the other,[6,8] because direct comparisons of both types of long-acting agents were limited or had a short duration.[10,11] Recently, however, results of a large multinational head-to-head comparison, the Prevention Of Exacerbations with Tiotropium (POET-COPD) trial, were published. This one-year trial in patients with moderate to very severe COPD and a history of at least one exacerbation in the previous year showed that tiotropium was more effective in preventing exacerbations than salmeterol.[12,13] The trial-based economic evaluation showed that tiotropium significantly reduced exacerbation-related costs, but total costs were higher than in the salmeterol group.[14] The costs per exacerbation avoided were estimated to be €1961, using the perspective of the German Statutory Health Insurance (SHI). The aim of the current study was to estimate the cost-effectiveness of tiotropium versus salmeterol in the Dutch setting. Due to the very small number of Dutch COPD patients included in the trial (n=2) a subgroup analysis on Dutch patients in the POET-COPD trial was not possible. Instead of such a trial-based analysis, a model-based analysis was done using a previously published COPD cost-effectiveness model.[15-17] The exacerbation probabilities and healthcare use in this model were updated with data from the POET-COPD trial.[13] This updated model was used to estimate the cost-effectiveness of tiotropium versus salmeterol in the Netherlands, to extrapolate results up to five years and to calculate quality-adjusted life-years (QALYs).

METHODS

Model structure

The Markov model used has been described in detail previously.[15-17] The model is a state-transition model that simulates how a cohort of COPD patients progresses over time. It has four states, three COPD severity states, moderate, severe and very severe COPD defined by the lung function boundaries of the GOLD guidelines,[6] and death. The starting distribution of patients over the three COPD severity states was based on Dutch data: 75% in moderate, 21% in severe and 4% in very severe COPD.[18] In each COPD severity state patients have a risk to experience a non-severe or severe exacerbation. The model has a cycle length of one month, which means that each month patients have a certain probability to move between states and experience an exacerbation. Healthcare costs, mortality rates and quality of life (utilities) were assigned to the COPD states and the exacerbations. The time horizon of the model can vary between one and five year. The model was validated in previous publications.[14,15]

The model is filled with data on the probability to have an exacerbation and the probability that an exacerbation is severe. In the POET-COPD trial an exacerbation was defined as an increase or new onset of more than one symptom (cough, sputum, wheezing, dyspnoea, chest tightness), with at least one symptom lasting at least three days requiring treatment with systemic steroids or antibiotics (non-severe or moderate exacerbation) or hospitalisation (severe exacerbation). Exacerbation data from the tiotropium group of the POET-COPD trial were synthesised with evidence on COPD exacerbations from previous tiotropium studies[10,19,20] by performing a Bayesian fixed-effects meta-analysis. The relative risks of salmeterol versus tiotropium obtained from the salmeterol-controlled tiotropium trials[10,13] were applied to the pooled exacerbation probabilities of tiotropium to obtain the probabilities for salmeterol. The exacerbation probabilities are shown in *table 1*. The risk of experiencing an exacerbation varies by COPD state and treatment group and was assumed to be constant over time.

The model is also filled with probabilities to move between states. These transition probabilities were not affected by the POET-COPD trial and remained the same as previously published.[17] The probabilities to move to another COPD severity stage for the first year were obtained from the pooled patient-level data of six tiotropium trials.[10,19,20] The transition probabilities for salmeterol were calculated in the same way as the exacerbation probabilities by applying the relative risks observed in the two trials directly comparing tiotropium and salmeterol with the transition probabilities of tiotropium.[9,12] The resulting probabilities to move to a more severe COPD state in the first year were slightly higher for salmeterol compared with tiotropium. The decline in lung function after the first year was assumed to be 52 ml per year in both treatment groups.[16]

Table 1. *Mean (SE) monthly exacerbation probabilities by treatment group after update with data from the POET-COPD trial using Bayesian fixed-effects meta-analysis**

	Probability to experience an exacerbation		Probability that the exacerbation is severe, given an exacerbation	
	Tiotropium	Salmeterol	Tiotropium	Salmeterol
Moderate COPD	.0483 (.002)	.0495 (.004)	.1098 (.014)	.1093 (.026)
Severe COPD	.0624 (.001)	.0681 (.002)	.1697 (.010)	.1776 (.015)
Very severe COPD	.0765 (.003)	.0844 (.004)	.2439 (.017)	.2738 (.028)

***Reproduced with permission of the European Respiratory Society.[14]**

The probabilities to die within each COPD severity state were derived from the Dutch all-cause age- and sex-specific mortality rates among COPD patients.[21,22]

Input data with regard to quality of life consisted of the utility values per COPD severity in the stable state[23] and the proportional reduction in the utility during an exacerbation. During the month in which patients experienced an exacerbation the utility value in the stable state was reduced by 15% for a non-severe exacerbation and by 50% for a severe exacerbation.

Perspective

The cost-effectiveness study for the Dutch setting was performed from two different perspectives: 1) the Dutch healthcare perspective, including all national healthcare insurance costs and 2) the societal perspective, including all national healthcare insurance costs, patient co-payments, travel expenses and costs of absence from paid work.

Resource use and costs

The model distinguishes two types of healthcare utilisation: healthcare use for maintenance treatment (*table 2*) and for a non-severe or severe exacerbation (*table 3*). Exacerbation-related resource use and medication use for maintenance treatment were obtained from all patients included in the trial-based cost-effectiveness study of the POET-COPD trial.[14] Other healthcare utilisation associated with maintenance treatment was based on Dutch data sources, which can be found in *table 2*. The number of GP visits for maintenance treatment of COPD was calculated as the total number of GP visits among COPD patients minus the average number of visits for age-matched controls without COPD as obtained from the PHARMO database[26] minus the exacerbation-related visits as observed in the POET-COPD trial. The number of visits to the respiratory specialist for maintenance treatment was based on the average number of visits to

Table 2. *Annual costs of maintenance treatment in the Netherlands, in 2011* €

Costs of maintenance therapy (per year)	Unit cost	Moderate COPD				Severe COPD				Very severe COPD			
		Resource use		Total cost		Resource use		Total costs		Resource use		Total costs	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Outpatient visits to general practitioner[26]	29.27	5.09	0.09	149.01	2.68	4.43	0.14	129.56	4.0	4.09	0.32	119.84	9.33
Home visits by general practitioners[26]	44.95	0.57	0.03	25.43	1.37	1.11	0.09	49.74	3.84	2.34	0.25	105.17	11.14
Outpatient visits to respiratory specialists[27,28]	75.27	0.26	0.05	19.26	4.14	2.37	0.21	178.66	15.90	2.37	0.21	178.66	15.90
Spirometries[24]	17.67	0.33	0.07	5.83	1.17	1.0	0.20	17.67	3.53	1.0	0.20	17.67	3.53
Influenza vaccination (%)[25]	15.71	0.73	0	11.48	0.05	0.73	0	11.48	0.05	0.73	0	11.48	0.05
Days antibiotics used*	0.53	2.75	0.34	1.46	0.18	2.67	0.39	1.42	0.21	1.34	0.26	0.71	0.14
Days systemic steroids used*	0.06	7.36	0.85	0.44	0.05	10.56	1.05	0.64	0.06	11.08	2.44	0.67	0.15
Days short-acting beta-agonists used*	0.17	6.73	0.82	1.18	0.14	8.87	0.98	1.55	0.17	9.95	2.30	1.74	0.40
Days short-acting anticholinergics used*	0.30	1.39	0.34	0.41	0.10	1.44	0.38	0.43	0.11	2.91	1.21	0.87	0.36
Days inhaled corticosteroids used*	0.68	141.23	2.99	95.47	2.02	156.38	3.24	105.72	2.19	139.72	7.15	94.45	4.83
Days theophylline used*	0.04	60.60	2.24	2.50	0.09	76.67	2.65	3.16	0.11	73.07	2.64	3.01	0.11
Days mucolytics used*,#	0.71	9.03	0.91	6.41	0.65	12.00	1.16	8.51	0.82	11.06	2.29	7.85	1.62
Days oxygen used*	4.34	0.86	0.26	3.73	1.13	3.71	0.63	16.09	2.73	5.81	1.72	25.20	7.46
Travel costs (km)*,#	0.21	7.39	1.48	1.55	0.31	21.48	4.30	4.49	0.90	21.12	4.22	4.42	0.88
Total costs healthcare perspective				316.21	5.74			516.11	17.56			559.47	23.57
Total costs societal perspective				324.16	5.79			529.12	17.60			571.73	23.64

*Source resource use: all patients in POET-COPD trial; #Costs only included using the societal perspective.

Table 3. *Costs per COPD exacerbation in the Netherlands, in 2011* €

Per exacerbation	Unit cost	Non-severe exacerbation				Severe exacerbation			
		Resource use		Costs		Resource use		Costs	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
ICU days	2282.23	na	na	na	na	0.76	0.18	1734.49	408.52
Non-ICU days	228.14	na	na	na	na	12.39	0.33	2825.92	75.90
Ambulance rides	346.05	na	na	na	na	0.31	0.02	107.27	5.88
Outpatient visits to general practitioners	29.27	0.58	0.01	17.10	0.42	0.40	0.03	11.72	0.81
Outpatient visits to respiratory specialists	75.27	0.60	0.02	44.86	1.23	0.46	0.03	34.93	2.13
Outpatient visits to non-respiratory specialists	75.27	0.04	0.01	3.12	0.39	0.07	0.01	4.99	0.80
Outpatient visits to other healthcare providers	37.64	0.03	0.01	1.13	0.26	0.03	0.01	1.13	0.30
ER visits not followed by hospital admission	157.86	0.04	0.03	6.31	0.47	0.20	0.02	31.57	2.53
Ambulance rides to ER	346.05	0.01	0.02	3.46	0.69	0.12	0.01	41.53	4.50
Days antibiotics	0.53	8.54	0.34	4.54	0.18	13.19	1.02	7.0	0.54
Days systemic steroids	0.06	6.82	0.38	0.41	0.02	14.89	1.25	0.90	0.08
Days short-acting beta-agonists	0.17	0.31	0.13	0.05	0.02	1.44	0.47	0.25	0.08
Days short-acting anticholinergics	0.30	0.39	0.13	0.12	0.04	2.73	0.34	0.82	0.10
Days inhaled corticosteroids	0.68	3.45	0.45	2.33	0.30	8.40	1.29	5.68	0.87
Days theophylline	0.04	2.02	0.36	0.08	0.01	11.13	1.43	0.46	0.06
Days mucolytics#	0.71	2.26	0.22	1.61	0.15	6.95	0.77	4.93	0.55
Travel costs (km)#	0.21	5.45	1.09	1.14	0.23	5.62	1.12	1.17	0.23
Costs for days absence paid work#	304.27	1.01	0.06	307.26	17.79	2.65	0.26	806.60	80.32
Total costs of exacerbation healthcare perspective				83.52	1.65			4808.67	415.59
Total costs of exacerbation societal perspective				393.52	17.87			5621.38	426.28

na=not applicable; #costs only included using the societal perspective.

specialists specified by level of dyspnoea,[27] the percentage of patients visiting the respiratory specialist[28] and the exacerbation-related visits to the respiratory specialist in the POET-COPD trial. Unit costs for contacts with the different healthcare providers were obtained from the Dutch costing manual[29] and updated to the year 2011.[30] The unit costs for an inpatient hospital day for COPD were obtained from a Dutch clinical trial.[31] All medication costs were based on the list prices of 2011 minus the clawback including 6% VAT as obtained from the Taxe (October 2011). The average costs of study medication were calculated as the weighted average costs per daily defined dose (DDD) of all available devices of either tiotropium or salmeterol using the total DDDs in the Netherlands as a weight. This resulted in an average cost per day of €1.35 for tiotropium and €0.91 for salmeterol. All medications were fully reimbursed, except for the mucolytics. Therefore medication costs from the healthcare and societal perspective were equal except for the mucolytics for which the costs were only included in the societal perspective.

Health outcomes

The main health outcomes of the model were the total number of non-severe and severe exacerbations and the total number of QALYs. The total number of QALYs was calculated as the sum of the annual number of life years (=number of patients alive) weighted by the quality of life during these years using the utility weights specified by COPD severity state. For each exacerbation a reduction in utility weights was applied.

Cost-effectiveness

The incremental cost-effectiveness ratios (ICERs) were calculated as the difference in total costs between the tiotropium and the salmeterol group divided by the difference in the number of QALYs or the difference in exacerbations resulting in the costs per QALY gained and the costs per exacerbation avoided, respectively.

Base-case analysis

The base-case analysis was performed for a one-year and five-year time horizon, both for the healthcare and the

societal perspective. In the five-year analysis costs were discounted with 4%, effects with 1.5%.[32]

Sensitivity analyses

Several one-way sensitivity analyses were performed on changes in the starting distribution of the patients over the COPD severity states (100% in either moderate, severe or very severe COPD), different methods of meta-analysis for the exacerbation probabilities (frequentist fixed- and random-effects meta-analysis) and different discount rates (0% or 4% discounting for both costs and effects). Furthermore, the impact of three other assumptions was tested: assuming no difference in exacerbation risk between tiotropium and salmeterol after one year, using different unit costs for an inpatient hospital day based on the Dutch costing manual (€478) and applying a 50% smaller reduction in utility due to an exacerbation. All one-way sensitivity analyses were performed from the healthcare perspective. The model had a fully probabilistic design, which means that uncertainty around the transition and exacerbation probabilities, utilities and costs was taken into account.[15] After making 5000 random draws from the probability distributions of the uncertain parameters, the model was run for each set of parameters. This resulted in 5000 different outcomes for effects and costs, which were plotted on cost-effectiveness planes (CE plane). A CE plane is an x-y diagram with the x-axis representing the difference in health outcome between tiotropium and salmeterol and the y-axis representing the difference in costs. The information in the CE plane was summarised in cost-effectiveness acceptability curves, which show the probability that the incremental cost-effectiveness ratio of tiotropium falls below a range of ceiling ratios. These ceiling ratios reflect the maximum the decision makers would be willing to invest to gain one QALY.

Table 4. *One-year and five-year results from the model-based cost-effectiveness analysis, healthcare perspective (costs in 2011 €)*

	Tiotropium*	Salmeterol*	Difference*
One year:			
Total exacerbations	0.647 (0.614-0.681)	0.716 (0.648-0.780)	-0.068 (-0.410-0.005)
Quality-adjusted life-years	0.747 (0.726-0.763)	0.736 (0.700-0.756)	0.011 (-0.019-0.049)
Costs of study medication	485 (473-491)	328 (313-332)	157 (144-173)
Costs of maintenance therapy	390 (371-410)	410 (378-443)	-19 (-57-18)
Exacerbation-related costs	495 (401-600)	621 (471-749)	-127 (-320-56)
Total costs	1370 (1268-1482)	1359 (1191-1544)	11 (-198-212)
Five year:			
Total exacerbations	3.189 (2.937-3.400)	3.624 (3.133-4.035)	-0.435 (-0.915-0.107)
Quality-adjusted life-years	3.355 (3.108-3.522)	3.276 (2.869-3.517)	0.079 (-0.272-0.520)
Costs of study medication	2130 (1987-2222)	1440 (1273-1525)	690 (514-885)
Costs of maintenance therapy	1889 (1726-2046)	1996 (1733-2226)	-107 (-386-212)
Exacerbation-related costs	2600 (2103-3148)	3459 (2581-4458)	-860 (-1970-178)
Total costs	6618 (5957-7296)	6895 (5757-8073)	-277 (-1586-1074)

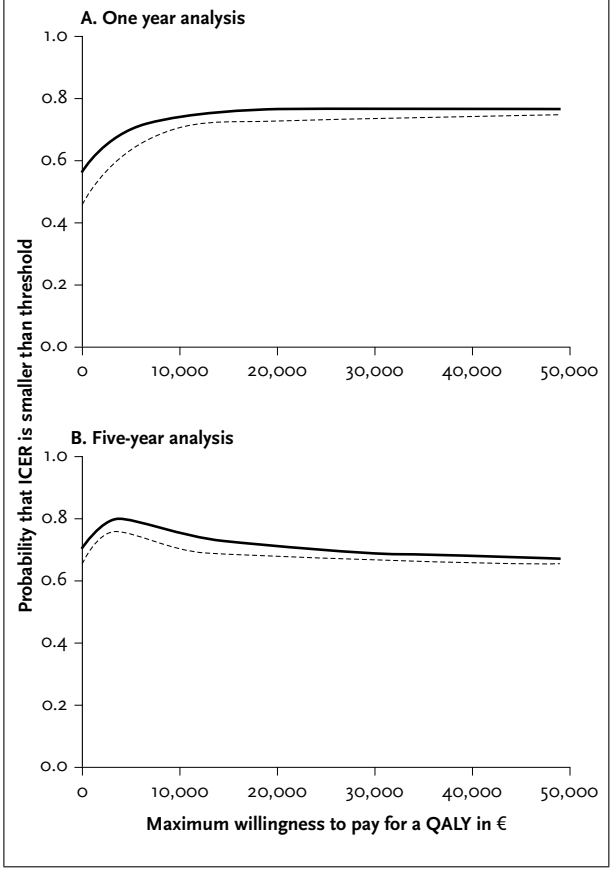
***Data are mean (95% uncertainty interval)**

RESULTS

One-year results

After one year, treatment with tiotropium resulted in 0.011 (95% uncertainty interval (UI) -0.019-0.049) more QALYs and 0.068 (95% UI -0.005-0.14) less exacerbations compared with salmeterol (*table 4*). The reduction in severe exacerbations was 0.025 (95% UI -0.003-0.055). As a result the total exacerbation-related costs were more than 20% lower in the tiotropium group compared with the salmeterol group. Hospitalisation-related exacerbation costs were reduced by 22%, while other exacerbation-related costs decreased by 12%. Costs for study medication were €157 (95% UI 144-173) higher for tiotropium. The total costs per patient from the healthcare perspective were €1370 (95% UI 1268-1482) in the tiotropium group and €1359 (95% UI 1191-1544) in the salmeterol group, resulting in a difference of €11 (95% UI -198-212). The incremental cost-effectiveness ratios were €162 for the cost per exacerbation avoided and €1015 for the costs per QALY. From a societal perspective the total costs per patient were €1628 (95% UI 1520-1747) for the tiotropium group and €1650 (95% UI 1463-1856) for the salmeterol group, a difference of €-22 (95% UI -251-197). In the tiotropium group costs for productivity loss due to an exacerbation were €33 (95% UI -16-83) lower compared with salmeterol. Because tiotropium dominated salmeterol from a societal perspective, i.e. was more effective and less costly, no ratios have been calculated. The CE plane from the healthcare perspective using QALYs as outcome showed that in 41% of the simulations treatment with tiotropium resulted in more effects and higher costs, while in 36% tiotropium was more effective and cost saving compared with salmeterol. Using exacerbations as outcome these percentages were 51% and 45%, respectively. *Figure 1* shows the acceptability curve for the costs per QALY from the two perspectives. For a maximum-willingness-to-pay for a QALY of €20,000, the probability that tiotropium would be cost-effective was 73% from a healthcare perspective and 76% from a societal perspective.

Figure 1. *Acceptability curve for the costs per QALY gained for A) one-year analysis and B) five-year analysis (dashed line: healthcare perspective, black line: societal perspective)*



Five-year results

The model results using a time horizon of five years showed that the gain in QALYs due to tiotropium was 0.079 (95% UI -0.272-0.520) compared with salmeterol (*table 4*). The total number of exacerbations was almost 14% lower in the tiotropium group than in the salmeterol group. The reduction in severe exacerbations was significant, 0.184 (95% UI 0.008-0.367). From a healthcare perspective the total five-year costs were €6618 (95% UI 5957-7296) for tiotropium and €6895 (95 UI 5757-8073) for salmeterol, a difference of €-277 (95% UI -1586-1074) (*table 4*). The higher costs of tiotropium were completely offset by the savings in exacerbation-related costs. From a societal perspective the difference in costs between tiotropium and salmeterol was €-409 (95% UI -2040-1180). Tiotropium reduced costs for productivity loss for exacerbations by €120 (95% UI-182-433) (12% reduction) compared with salmeterol. Both from a healthcare and societal perspective, tiotropium dominated salmeterol, so no cost-effectiveness ratios were calculated. The acceptability curve for the five-year analysis (*figure 1*) showed that the probability that tiotropium was cost-effective at a threshold value of €20,000 per QALY was 67% from a healthcare perspective and 70% from a societal perspective.

One-way sensitivity analyses

One-year results were most sensitive to the severity distribution assumed at baseline. The incremental cost-effectiveness ratios for both the costs per QALY and the costs per exacerbation avoided increased when all patients had moderate COPD at start of treatment, whereas tiotropium was dominant over salmeterol when all patients had severe or very severe COPD at the start. Using the exacerbation probabilities based on random-effects meta-analysis and using the higher unit costs of an inpatient hospital day also resulted in tiotropium being more effective and less costly than salmeterol. For all remaining one-year sensitivity analyses the ICERs were well below €20,000 per QALY. For the five-year analyses tiotropium was more effective and less costly in all sensitivity analyses, except one. If no exacerbation benefit for tiotropium was assumed after the first year, the costs per QALY would become €130.

DISCUSSION

The current study aimed to estimate the cost-effectiveness of tiotropium versus salmeterol in the Dutch setting. From a healthcare perspective the one-year total costs for tiotropium were €11 (95% UI -198-212) higher. The higher medication costs (€157 per patient) for tiotropium were for more than 80% compensated by a reduction in costs for COPD exacerbations. The ICERs were €162 for the costs per exacerbation avoided and €1015 for the costs per QALY. If the reduction in costs due to productivity loss during exacerbations in the tiotropium group were also included, as was done in the analysis from the societal perspective, the higher medication costs for tiotropium would be completely compensated, resulting in tiotropium being more effective and less costly than salmeterol.

Using a five-year time horizon, the total costs per patient from a healthcare perspective were €277 (95% UI -1074;1586) lower for tiotropium compared with salmeterol. The higher medication costs of tiotropium (€690 per patient in five years) were fully offset by the reduction in costs of COPD exacerbations. From a societal perspective the total five-year costs in the tiotropium group were €409 (95% UI -2040-1180) lower compared with the salmeterol group. As a result tiotropium dominated salmeterol irrespective of the perspective used. Five-year results were better than one-year results because in the five-year analyses the impact of disease progression of COPD was also taken into account. Because the reduction in exacerbations in tiotropium compared with salmeterol

was greater in patients with severe and very severe COPD, the difference in effect between tiotropium and salmeterol became greater when patients progressed towards more severe stages of COPD.

In all one-year sensitivity analyses, the ICER remained below €20,000. The results were most sensitive to the severity of COPD at the start of treatment, i.e. tiotropium was dominant in patients with severe and very severe COPD, whereas in moderate COPD the costs per exacerbation avoided were €527 and the costs per QALY €3200. Results were also sensitive to the unit costs for an inpatient hospital day. Using the reference unit costs of a non-ICU hospital day from the Dutch costing manual[29] (€478 per day in 2011) resulted in tiotropium dominating salmeterol. Because we had indications that the unit costs for a non-ICU inpatient hospital day for COPD were lower than this reference price, we used a lower unit cost of €228 in the base-case analysis. This lower estimate of the costs of an inpatient hospital day was based on a clinical trial investigating the effectiveness of early assisted discharge in patients hospitalised for a COPD exacerbation.[31] Because the patients in that trial had exacerbations that were probably less severe than the average exacerbation that requires a hospital admission, our estimate of the unit costs used in the base-case analysis is likely to be a minimum estimate of the costs of an inpatient hospital day for COPD. Therefore, the results of the base-case analyses are conservative. The five-year sensitivity analyses showed that tiotropium was dominant in all cases, except one. Results were most sensitive to the assumption that was made about the difference in exacerbation probabilities between the two treatments after the first year. In the base-case this difference was assumed to remain constant during year 2 to 5. If, in the extreme case, we did not assume any additional exacerbation benefit of tiotropium compared with salmeterol after the first year, tiotropium would no longer be dominant. The costs per QALY would become €130, still a very low ratio.

The updated model used in the current study was validated by using the exacerbation probabilities, COPD severity distribution and time horizon of the POET-COPD trial as input for the model.[14] Comparison of the model results with the outcomes of the trial showed that the model was able to reproduce the difference in total number of exacerbations and severe exacerbations in the trial. The resulting cost per QALY gained was also comparable.[14] The model could not be validated for the five-year time horizon. The decline in lung function of 52 ml per year that was assumed after the first year may be relatively high given recent publications.[33-35] The impact of this assumption on the results is, however, limited because the same annual decline was used for both treatment options.

A recent review on pharmacological maintenance treatment of COPD found six studies investigating the cost-effectiveness of tiotropium versus salmeterol, one for the Dutch setting.[36] All of these studies were modelling studies, mostly based on the same model as used in this study. Tiotropium was found to be more effective and less costly in four out of the six studies, including the study for the Netherlands. The other two studies reported cost-effectiveness ratios below €4118 per QALY gained. The difficulty with these modelling studies was that input data for the difference in exacerbations were obtained from studies directly comparing tiotropium and salmeterol that had a short duration and were underpowered to detect a difference in COPD exacerbations.[10] The current study showed that update of the input data of the model with exacerbation data from the large POET-COPD trial did not change the conclusions. Tiotropium was still very cost-effective compared with salmeterol and even cost saving using a societal perspective or a five-year time horizon.

The severity distribution for COPD used in the current version of the model was based on the degree of airflow limitation. Recently the GOLD committee proposed a new grading of COPD severity based on airflow obstruction, symptoms and exacerbations.[37] Although the new classification reflects the complexity of COPD better than the classification based on airflow limitation alone, evidence on the prognostic value of the new classification in predicting future health outcomes is lacking. If in the future treatment effects and cost-effectiveness results are found to be different between the severity classes of this new classification, changes in the structure of the model need to be considered.

Up to the publication of the POET-COPD trial most international and national guidelines did not specify a preference for either long-acting anticholinergics or long-acting beta-agonist as evidence on difference in exacerbations was still limited. Only the NHG practice guideline 'COPD' reported a preference for tiotropium in a specific subgroup of patients.[7] The new available information on the difference in effects between tiotropium and salmeterol from the POET-COPD trial and the difference in costs from the current study can contribute to future guideline development and policy making for COPD in the Netherlands.

In conclusion, both over a one- and five-year time horizon tiotropium was found to reduce exacerbations compared with salmeterol among patients with moderate to very severe COPD, leading to a reduction in exacerbation costs. After one-year the total costs for tiotropium were slightly higher than for salmeterol leading to a cost per QALY of

€1015, which is regarded to be very cost-effective in the Netherlands. After five years the higher drug costs for tiotropium were completely compensated by the savings in exacerbation-related costs, resulting in tiotropium being more effective and cost saving.

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REFERENCES

1. Bischoff EW, Schermer TR, Bor H, Brown P, van Weel C, van den Bosch WJ. Trends in COPD prevalence and exacerbation rates in Dutch primary care. Br J Gen Pract. 2009;59:927-33.
2. Gommer AM, Poos MJJC, eds. Cijfers COPD (Prevalentie, Incidentie En Sterfte) Uit VTV 2010. in Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, Bilthoven, 2010.
3. van der Lucht F, Polder JJ, eds. Van Gezond Naar Beter. Kernrapport Van De Volksgezondheid Toekomst Verkenning VTV-2010. National Institute of Public Health and the Environment (RIVM), Bilthoven, version 1.0, 25 March 2010.
4. Poos MJJC, ed. Waaraan Overlijden Mensen in Nederland? in: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, Bilthoven, 2008.
5. Gommer AM, Hoeymans N, Poos MJJC, eds. Wat is De Ziektelast in Nederland? in: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. RIVM, Bilthoven, 2010.
6. Global Initiative for Chronic Obstructive Lung Disease. Workshop Report: Global Strategy for the Diagnosis, Management and Prevention of COPD: Updated 2009; http://www.goldcopd.com (Accessed September 2009).
7. NHG-Standaard COPD. Nederlands Huisartsen Genootschap, Utrecht, 2007.
8. Richtlijn Diagnostiek En Behandeling Van COPD. Kwaliteitsinstituut voor de Gezondheidszorg CBO, Utrecht, 2010.
9. Diamant Z, Tarasevych S, Clarke GW. New and existing pharmacotherapeutic options for persistent asthma and COPD. Neth J Med. 2011;69:486-99.
10. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax. 2003;58:399-404.
11. Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther. 2005;18:397-404.
12. Beeh KM, Hederer B, Glaab T, et al. Study design considerations in a large COPD trial comparing effects of tiotropium with salmeterol on exacerbations. Int J Chron Obstruct Pulmon Dis. 2009;4:119-25.
13. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD. N Engl J Med. 2011;364:1093-103.
14. Hoogendoorn M, Al MJ, Beeh KM, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. Eur Respir J.; Published ahead of print June 14 2012, doi:10.1183/09031936.00027212.
15. Oostenbrink JB, Rutten-van Molken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health. 2005;8:32-46.
16. Rutten-van Molken MP, Oostenbrink JB, Miravitlles M, Monz BU. Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain. Eur J Health Econ. 2007;8:123-35.
17. Oostenbrink JB, Al MJ, Oppe M, Rutten-van Molken MP. Expected value of perfect information: an empirical example of reducing decision uncertainty by conducting additional research. Value Health. 2008;11:1070-80.
18. Hoogendoorn M, Feenstra TL, Schermer TR, Hesselink AE, Rutten-van Molken MP. Severity distribution of chronic obstructive pulmonary disease (COPD) in Dutch general practice. Respir Med. 2006;100:83-6.
19. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19:217-24.
20. Vincken W, van Noord JA, Greefhorst AP, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J. 2002;19:209-16.
21. Feenstra TL, Van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Molken MP. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med. 2001;164:590-6.
22. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, et al. A dynamic population model of disease progression in COPD. Eur Respir J. 2005;26:223-33.
23. Rutten-van Molken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest. 2006;130:1117-28.
24. Richtlijn Ketenzorg COPD. Stichting Ketenkwaliteit COPD. Van Zuiden Communications BV, Alphen aan den Rijn, 2005.
25. Tacken M, Mulder J, Visscher S, et al., eds. Monitoring Vaccinatiegraad Nationaal Programma Grieppreventie 2009. LINH/Scientific Institute for Quality of Healthcare, Nijmegen, 2010.
26. PHARMO Institute. Healthcare Utilization for Patients with a COPD Diagnosis (Known by GP) by GOLD Stage. PHARMO Report, Utrecht, 2011.
27. van Houtum L, Spreeuwenberg P, Heijmans M, eds. Zorgsituatie Van Mensen Met COPD. Rapportage 2010. NIVEL, Utrecht, 2011.
28. Heijmans MJWM, Spreeuwenberg P, Rijken PM, eds. Monitor Zorg- En Leefsituatie Van Mensen Met Astma En Mensen Met COPD. Trends En Ontwikkelingen Over De Periode 2001-2008. NIVEL, Utrecht, 2009.
29. Hakkaart-van Roijen L, Tan S, Bouwmans C, eds. Handleiding Voor Kostenonderzoek. Methoden En Referentieprijzen Voor Economische Evaluaties in De Gezondheidszorg. Geactualiseerde Versie 2010. Erasmus Universiteit, iMTA, Rotterdam, 2010.
30. Consumentenprijzen; prijsindex 2006=100. 2011; http://statline/cbs.nl/ (Accessed Nov 2011).
31. Utens CM, Goossens LM, Smeenk FW, et al. Effectiveness and cost-effectiveness of early assisted discharge for chronic obstructive pulmonary disease exacerbations: the design of a randomised controlled trial. BMC Public Health. 2010;10:618.
32. Rodenburg-van Dieten HEM, ed. Guidelines for Pharmaco-Economic Research. Dutch Healthcare Insurance Board, Diemen, 2005.
33. Vestbo J, Edwards LD, Scanlon PD, et al., ECLIPSE Investigators. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365:1184-92.
34. Tashkin DP, Celli B, Senn S, et al., UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359: 1543-54.
35. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178:332-38.
36. Rutten-van Mölken MPMH, Goossens LMA. The cost-effectiveness of pharmacological maintenance treatment of chronic obstructive pulmonary disease (COPD): a review of evidence and methodology issues. PharmacoEconomics. 2012;30:1-32.
37. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2011; http://www.goldcopd.com (Accessed, May 2012).

ORIGINAL ARTICLE

Unintentional weight loss is the most important indicator of malnutrition among surgical cancer patients

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ABSTRACT

Background: Disease-related malnutrition is highly prevalent in hospital patients and varies from 25-40%. Early nutritional screening of patients at admission helps to improve recognition of malnourished patients to allow early interventions and enhance clinical outcomes.

Method: A total of 104 preoperative surgical patients with oesophageal (34), stomach (17) or pancreatic cancer (53) were recruited in our study. The risk of malnutrition was examined using the quick-and-easy Malnutrition Universal Screening Tool (MUST). Anthropometric data and information on percent weight change over the past six months, unintentional weight loss, dietician referrals, and history of nutritional intervention were collected.

Results: A total of 75% of our participants were at high malnutrition risk with a mean (±SD) percentage weight loss of 5.18 (±6.23)%, despite a mean BMI of 26.09 (±5.73) kgm^{-2}. Participants with a significantly higher percent weight loss, unintentional weight loss, dietician referral and nutritional intervention had a higher risk of malnutrition ($p<0.05$). Presence of unintentional weight loss was the only significant predictor (OR 3.22; 95% CI 1.23, 8.40) associated with risk of malnutrition after adjusted for all confounders.

Conclusion: In conclusion, our findings highlight the importance of routine screening of malnutrition in oncology patients. Medical personnel must be aware that unintentional weight loss is an important predictor of malnutrition risks even if the patient's BMI is not suggestive of malnutrition.

KEYWORDS

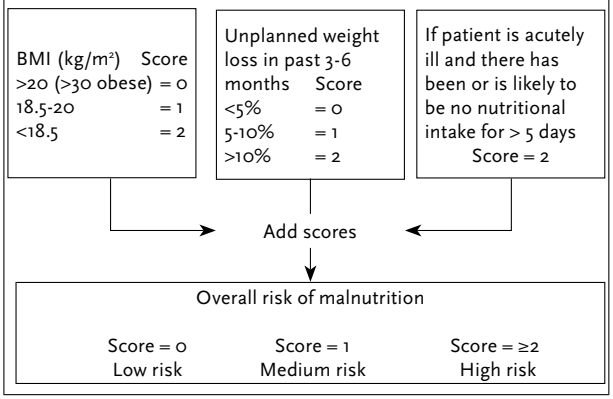
Malnutrition, Malnutrition Universal Screening Tool (MUST), weight loss, cancer

INTRODUCTION

Although a large number of studies have shown high prevalence rates (up to 40%) of disease-related malnutrition in healthcare organisations, malnourished patients often remain unrecognised in these settings.[1-5] Malnutrition can lead to many complications such as delayed wound healing, increased postoperative morbidity and prolonged hospitalisation.[6-8] Kruizenga *et al.* emphasised that early screening of patients at the time of diagnosis may improve recognition of malnourished patients by 50-80% and reduce the length of hospital stay.[9,10]

Of the many nutritional assessment methods, the Subjective Global Assessment (SGA), the Malnutrition Universal Screening Tool (MUST) (*figure 1*) and the Nutritional Risk Index (NRI) are most commonly used in hospital settings. The Patient Generated-Subjective Global Assessment (PG-SGA) was adapted from the SGA and validated for nutritional status assessment in oncology patients.[11] MUST scores were found to be consistent with PG-SGA scores,[12] demonstrating the validity and effectiveness of MUST in correctly identifying malnourished patients with cancer.

Figure 1. *MUST is composed of three components: body mass index score [BMI = weight (kg)/ height (m²)], a weight loss score and an acute illness component lasting longer than five days with or likely to have no nutritional intake. The summed scores were divided into three degrees and the risk of malnutrition can be assessed based on the summed scores. For further information on MUST and management guidelines, see http://www.bapen.org.uk/screening-for-malnutrition/must/introducing-must*



Another study assessing the feasibility of use of nutritional assessment methods has recommended the MUST as a routine nutrition evaluation tool because it is simple to use, rapid (within 3 to 5 minutes)[7,13-14] and less expensive when compared with SGA and NRI.[15] It has good predictive validity in examining the association of malnutrition with length of stay, mortality and hospital cost,[8,16] with a higher sensitivity, specificity, positive predictive value and negative predictive value than the NRI[15] when the SGA was used as a benchmark.

Weight loss was highlighted as a common condition among patients with cancer at the time of diagnosis as early as 30 years ago.[17] In the outpatient setting, one in five patients with colorectal cancer were malnourished (weight loss >10%) when they first entered the secondary healthcare system.[18] Cancer-associated malnutrition mainly affects patients with certain cancers (e.g. gastrointestinal and pancreatic cancer) and has a significant negative impact on prognosis and survival. Cachexia is most prevalent in patients with stomach or pancreatic cancer, in which at least 80% of patients present with or develop cachexia that deteriorates further after the time of diagnosis.[19] These detrimental effects demonstrate the importance of early assessment of nutritional status among patients with cancers.

The general objective of our study was to assess the risk of malnutrition in preoperative surgical patients with gastrointestinal and pancreatic cancer using the malnutrition universal screening tool (MUST). The specific objectives of the study were:

1. To define and compare the prevalence of malnutrition using BMI <20 kgm^{-2} and MUST among preoperative surgical patients.
2. To describe the patient-dependent (age, gender, and body mass index), tumour-dependent (tumour location), and intervention-related (dietician referral and nutritional intervention) indicators among preoperative surgical patients.
3. To study the association of patient-dependent, tumour-dependent and intervention-related indicators with malnutrition risk among preoperative surgical patients.

PATIENTS AND METHODS

From January to October 2011, 104 consecutive surgical patients were recruited in the study. The eligibility criteria included adult outpatients with oesophageal, stomach, and pancreatic cancer presenting for diagnosis, therapy or follow-up to the surgery unit of the University Medical Centre Utrecht, the Netherlands. Patients were excluded from the study when they were unable to give informed consent. The study protocol was approved by the Medical Ethics Research Committee of University Medical Centre Utrecht, the Netherlands.

In this survey, we chose to screen the nutritional status of the patients using the MUST (*figure 1*). This tool involves assessment of body mass index (BMI), unintentional weight loss in the preceding three to six months and presence of an acute disease resulting in absence of dietary intake for more than five days (or likely to result in no dietary intake for more than five days). The patients in this study were categorised into low (MUST score of 0 and 1) or high risk of malnutrition (MUST score of 2 or more). We combined the intermediate risk with the low-risk group due to small sample size and no active treatment was advocated for either group.[20] Nurses involved in this study received training prior to commencement of the study.

Body weight and height were measured by trained nurses according to standard procedures. If weight and height could not be measured, self-reported measurements were used to estimate underweight, obesity and overall malnutrition risk. The presence of dietician referral was sought and recorded. Throughout the study period, all information obtained was stored on an electronic database system, which was subsequently retrieved for statistical analyses.

Statistical analyses

All data were stored, structured and analysed using the SPSS for Windows version 16. Descriptive statistical methods were used to express means, standard deviations,

percentages and frequencies. The associations between risk factors and malnutrition were analysed using logistic regression. Odds ratios (OR) with 95% confidence intervals (CI) were reported where appropriate. Significant level was preset at 0.05.

RESULTS

A total of 104 patients were recruited. The patients were affected by solid tumours, the mean age was 64.7 (±SD 10.8) years, the men-to-women ratio was 1.5, the mean BMI was 26.2 (5.6) kgm^{-2}, the mean percentage weight loss was -2.7 (6.0) % and the mean MUST score was 2.0 (1.0).

Table 1 describes the characteristics of patients according to gender. Of note, a majority of patients were more than 65 years (58.7%), had a body mass index of more than 20 kgm^{-2} (95.2%), experienced unintentional weight loss (64.4%), had a dietician referral (55.8%), and underwent nutritional intervention (51.9%). The percentage of patients with pancreatic cancer was the highest (51.0%), followed by oesophageal cancer (32.7%) and stomach cancer (16.3%).

The prevalence of malnutrition was 75% and 4.8% using MUST and BMI, respectively. The mean BMI of those with malnutrition was in the overweight category (>25 kgm^{-2}) and mean percent weight loss was about 5% (*table 2*). A significant mean difference of percent weight loss ($p<0.05$) was observed between groups of patient with high risk and low risk of malnutrition.

Table 1. *Characteristics of patients according to gender*

Variables	Male	Female	Total	P
Patient, n (%)	63 (60.6)	41 (39.4)	104 (100.0)	
Age (years)				0.984
<65	26 (41.3)	17 (41.5)	43 (41.3)	
≥65	37 (58.7)	24 (58.5)	61 (58.7)	
Body mass index (kg/m^2)				0.335
<20.0	2 (3.2)	3 (7.3)	5 (4.8)	
≥20.0	61 (96.8)	38 (92.7)	99 (95.2)	
Tumour location				0.888
Oesophagus	21 (33.3)	13 (31.7)	34 (32.7)	
Stomach	11 (17.5)	6 (14.6)	17 (16.3)	
Pancreas	31 (49.2)	22 (53.7)	53 (51.0)	
Unintentional weight loss				0.278
Yes	38 (60.3)	29 (70.7)	67 (64.4)	
No	25 (39.7)	12 (29.3)	37 (35.6)	
Dietician referral				0.118
Yes	39 (61.9)	19 (46.3)	58 (55.8)	
No	24 (38.1)	22 (53.7)	46 (44.2)	
Nutritional intervention				0.187
Yes	36 (57.1)	18 (43.9)	54 (51.9)	
No	27 (42.9)	23 (56.1)	50 (48.1)	

Table 2. *Characteristics of different patient groups based on the risk of malnutrition (mean ± SD)*

Variables	High risk (n=78)	Low risk (n=26)	Mean difference (95% CI)
BMI (kg/m^2)	26.09 ± 5.73	26.63 ± 5.09	0.54 (-1.96,3.05)
Percent weight loss (%)	5.18 ± 6.23	1.26 ± 4.38	3.92 (1.70, 6.14)

Table 3. *Association of patients' characteristics with nutritional status classified by MUST*

Variable	High risk	Low risk	p
Age (years)			0.135 (NS)
<65	29 (67.4)	14 (32.6)	
≥65	49 (80.3)	12 (19.7)	
Sex, n (%)			0.297 (NS)
Male	45 (71.4)	18 (28.6)	
Female	33 (80.5)	8 (19.5)	
Body mass index, n (%)			0.186 (NS)
<20	5 (100.0)	0 (0)	
≥20	73 (73.7)	26 (26.3)	
Tumour location			0.830 (NS)
Oesophagus	25 (73.5)	9 (26.5)	
Stomach	12 (70.6)	5 (29.4)	
Pancreas	41 (77.4)	12 (22.6)	
Unintentional weight loss, n (%)			0.007
Yes	56 (83.6)	11 (16.4)	
No	22 (59.5)	15 (40.5)	
Dietician referral			0.040
Yes	48 (82.8)	10 (17.2)	
No	30 (65.2)	16 (34.8)	
Nutritional therapy			0.013
Yes	46 (85.2)	8 (14.8)	
No	32 (64.0)	18 (36.0)	

Table 3 shows the association of nutritional status classified by MUST with patients' characteristics. Patients who had unintentional weight loss (83.6%), at least one dietician referral (82.8%) and nutritional intervention (85.2%) were significantly associated with a high risk of malnutrition. All significant variables were further analysed using multiple logistic regression. After being adjusted for confounders, unintentional weight loss was the only significant predictor of risk of malnutrition, with an adjusted OR of 3.22 (95% CI 1.23, 8.40) (*table 4*).

DISCUSSION

To our best knowledge, this is the first study to clinically assess the risk of malnutrition among surgical patients with gastrointestinal and pancreatic cancer using MUST as the mode of assessment. The results of our

Table 4. *Crude and adjusted odds ratio of patient-dependent and intervention-related indicators with risk of malnutrition*

Variables		Crude OR	95% CI	Adjusted OR	95% CI
Unintentional weight loss	Yes	3.47	1.38-8.72	3.22	1.23-8.40
	No	1.00		1.00	
Dietician referral	Yes	2.56	1.03-6.38	0.39	0.05-3.34
	No	1.00		1.00	
Nutritional intervention	Yes	3.23	1.25-8.34	6.65	0.76-58.3
	No	1.00		1.00	

study show that three out of four patients in the study population presenting to the surgery outpatient clinic had malnutrition, a figure which is high and should be recognised. We identified unintentional weight loss as an important predictor of malnutrition risks even if the patient's BMI was not suggestive of malnutrition. Weight loss is strongly associated with poor outcomes across all stages of cancer.[21] The negative nitrogen balance underlying cancer cachexia leads to a significant wasting of skeletal muscle. Muscle loss jeopardises respiratory function, and impairs patient mobility and performance status.[22]

In our study, many patients with malnutrition and weight loss would be missed if BMI alone was used as a single measure of malnutrition risk. A similar observation has also been seen in other studies,[18,23] which suggested that BMI may be a poor indicator of nutritional risk in this group of patients. The principal limiting factor in the use of BMI is an artificial increase in body weight due to fluid retention, which is a common complication seen in cancer patients.[24]

A significant 82.8% of high-risk patients having had dietician referral suggested that early dietician referral for a suspected malnourished patient is crucial to improve clinical outcome. Many studies have shown that, beyond a certain point, starvation, weight loss and malnutrition result in progressive deterioration in both mental and physical function leading to eventual death.[25] It must be noted that nutritional intervention is not necessarily beneficial as malnutrition can be an inevitable consequence of progressive disease and may not be reversible by nutrition alone.[26] However, a substantial volume of evidence shows that early nutritional support is beneficial in certain groups of patients with increased risk of developing malnutrition.[25,27]

The small number of patients in the intermediate group (4.8%) may suggest that the MUST can discriminate very effectively between a high-risk and the low-risk group, but is less effective for the intermediate group. Until a new diagnostic approach is ascertained, MUST is an effective and validated means for identifying patients at malnutrition risk.[21,22,24,28-31] It is effective as the results are linked to a pathway of interventions appropriate for patient care. Early detection of nutritional risk would permit early intervention and improve clinical outcome.[8]

The findings of our research study reflect the urgent need for increased awareness of surgeons, nursing staff, and dieticians to the problem of unintentional weight loss among oncology patients. The high prevalence of malnutrition and associated poorer clinical outcome as suggested in many studies highlights the importance of routine screening with MUST in oncology patients as early intervention results in improved outcome.[3,32] Medical personnel must be aware that malnutrition afflicts even patients whose BMI is not suggestive of malnutrition

This study faced several limitations that need to be recognised. Our limited sample size did not allow comparison of various subgroups of patients, such as those who were young versus old, and the outcome of patients in the medium-risk group. The small sample size may have overestimated the effect of malnutrition risks. MUST may not be specifically designed for older adults as compared with other tools such as the Mini Nutritional Assessment (MNA). Use of MUST may be difficult among patients with communication difficulties such as dementia, delirium and hearing impairment. However, our study is one of the few that assessed malnutrition among gastrointestinal and pancreatic cancer patients in the surgery unit. We recommend the MUST as a simple and rapid tool in routine screening of nutritional risk in cancer patients.

CONCLUSIONS

In summary, the present study demonstrates that there is a high prevalence of malnutrition in patients with gastrointestinal and pancreatic cancer based on MUST. This highlights the importance of routine screening with MUST in oncology patients. Presence of unintentional weight loss is the only significant predictor of risk of malnutrition. Medical personnel must be aware that malnutrition afflicts even patients whose BMI is not suggestive of malnutrition. Identifying patients at risk is easy and feasible using MUST. After identification of patients at risk for malnutrition, thorough nutritional assessment must be performed.

AUTHOR'S NOTE

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REFERENCES

1. Corish CA, Kennedy NP. Undernutrition in hospitals. Br J Nutr. 2001;85:509-10.
2. Edington J, Boorman J, Durrant ER, et al. Prevalence of malnutrition on admission to four hospitals in England. The Malnutrition Prevalence Group. Clin Nutr. 2000;19:191-5.
3. Kelly IE, Tessier S, Cahill A, et al. Still hungry in hospital: identifying malnutrition in acute hospital admissions. QJM. 2000;93:93-8.
4. Kyle UG, Pirlich M, Schuetz T, Luebke HJ, Lochs H, Pichard C. Prevalence of malnutrition in 1760 patients at hospital admission: a controlled population study of body composition. Clin Nutr. 2003;22:473-81.
5. Susan A J. Incidence and recognition of malnutrition in hospital: J. P. McWhirter and C. R. Pennington BMJ. 1994; 308: 945-8. Clin Nutr. 1994;13:267-8.
6. Elia M, Zellipour L, Stratton RJ. To screen or not to screen for adult malnutrition? Clin Nutr. 2005;24:867-84.
7. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN Guidelines for Nutrition Screening 2002. Clin Nutr. 2003;22:415-21.
8. Kyle UG, Kossovsky MP, Karsegard VL, Pichard C. Comparison of tools for nutritional assessment and screening at hospital admission: A population study. Clin Nutr. 2006;25:409-17.
9. Kruizenga HM, Seidell JC, de Vet HCW, Wierdsma NJ, van Bokhorst–de van der Schueren MAE. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ©). Clin Nutr. 2005;24:75-82.
10. Kruizenga HM, Van Tulder MW, Seidell JC, Thijs A, Ader HJ, Van Bokhorst-de van der Schueren MA. Effectiveness and cost-effectiveness of early screening and treatment of malnourished patients. Am J Clin Nutr. 2005;82:1082-9.
11. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
12. Boléo-Tomé C, Monteiro-Grillo I, Camilo M, Ravasco P. Validation of the Malnutrition Universal Screening Tool (MUST) in cancer. Br J Nutr. 2012;108:343-8.
13. Clinical Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients, 2009. JPEN. 2009;33:255-9.
14. van Venrooij LMW, de Vos R, Borgmeijer-Hoelen AMMJ, Kruizenga HM, Jonkers-Schuitema CF, de Mol BAMJ. Quick-and-easy nutritional screening tools to detect disease-related undernutrition in hospital in- and outpatient settings: A systematic review of sensitivity and specificity. E Spen Eur E J Clin Nutr Metab. 2007;2:21-37.
15. Tu MY, Chien TW, Chou MT. Using a nutritional screening tool to evaluate the nutritional status of patients with colorectal cancer. Nutr Cancer. 2012;64:323-30.
16. Green SM, Watson R. Nutritional screening and assessment tools for use by nurses: literature review. J Adv Nurs. 2005;50:69-83.
17. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69:491-7.
18. Burden ST, Hill J, Shaffer JL, Todd C. Nutritional status of preoperative colorectal cancer patients. Journal of human nutrition and dietetics. Br Dietetic Assoc. 2010;23:402-7.
19. Tisdale MJ. Pathogenesis of cancer cachexia. J Support Oncol. 2003;1:159-68.
20. Ben-Ishay O, Gertsenzon H, Mashiach T, Kluger Y, Chermesh I. Malnutrition in Surgical Wards: A Plea for Concern. Gastroenterol Res Pract. 2011;2011. Epub 2010 Aug 3.
21. Vigano A, Bruera E, Jhangri GS, Newman SC, Fields AL, Suarez-Almazor ME. Clinical survival predictors in patients with advanced cancer. Arch Int Med. 2000;160:861-8.
22. MacDonald N, Easson AM, Mazurak VC, Dunn GP, Baracos VE. Understanding and managing cancer cachexia. J Am Coll Surg. 2003;197:143-61.
23. Corish CA, Kennedy NP. Protein–energy undernutrition in hospital in-patients. Br J Nutr. 2000;83:575-91.
24. Campillo B, Paillaud E, Uzan I, et al. Value of body mass index in the detection of severe malnutrition: influence of the pathology and changes in anthropometric parameters. Clin Nutr. 2004;23:551-9.
25. Allison S.P. The uses and limitations of nutritional support: The Arvid Wretlind Lecture given at the 14th ESPEN Congress in Vienna, 1992. Clin Nutr. 1992;11:319-30.
26. MacFie J. Ethical and legal considerations in the provision of nutritional support to the perioperative patient. Curr Opin Clin Nutr Metab Care. 2000;3:23-9.
27. Satyanarayana R, Klein S. Clinical efficacy of perioperative nutrition support. Curr Opin Clin Nutr Metab Care. 1998;1:51-8.
28. General Surgery Program Abstracts. ANZ J Surg. 2012;82:59-76.
29. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet. 368:666-78.
30. BAPEN. Screening for Malnutrition: A Multidisciplinary Responsibility, Development and Use of the Malnutrition Universal Screening Tool (MUST) for Adults. Malnutrition Advisory Group (MAG), a Standing Committee of BAPEN. 2003.
31. Heymsfield SB, Wang Z, Baumgartner RN, Dilmanian FA, Ma R, Yasumura S. Body composition and aging: a study by in vivo neutron activation analysis. J Nutrition. 1993;123(2 Suppl):432-7.
32. Lean M, Wiseman M. Malnutrition in hospitals. Br Med J (Clinical research ed). 2008;336:290.

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CASE REPORT

Idiopathic giant oesophageal ulcer and leucopoenia after renal transplantation

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ABSTRACT

A 45-year-old male recipient of a renal allograft was admitted because of a giant oesophageal ulcer coinciding with leucopoenia. An extensive workup revealed no explanation for the ulcer and leucopoenia. Our final diagnosis by exclusion was an idiopathic giant oesophageal ulcer and late-onset neutropenia as consequences of rituximab induction therapy given during the transplant procedure. The patient fully recovered after treatment with prednisone. However, after four months, the ulcer and leucopoenia recurred and again successfully responded to treatment with prednisone.

KEYWORDS

Idiopathic giant oesophageal ulcer, kidney transplantation, late-onset neutropenia, rituximab

What was known on this topic?

- Idiopathic giant oesophageal ulcers were initially reported in patients with AIDS and later on also in other immunocompromised patients.
- An idiopathic giant oesophageal ulcer is a diagnosis by exclusion.
- Patients with an idiopathic giant oesophageal ulcer can recover soon after starting steroids.
- Late-onset neutropenia might develop after administration of rituximab.

What does this case report add?

- The concurrence of leucopoenia and idiopathic giant oesophageal ulcer points to the use of rituximab as a common pathogenetic mechanism.
- An idiopathic oesophageal ulcer has never been reported before as an adverse event of rituximab.

INTRODUCTION

Ulceration and inflammation of the oesophagus are frequently seen in immunocompromised patients, such as transplant recipients, and have a comprehensive differential diagnosis.[1] Gastro-oesophageal reflux, infections, neoplasms, systemic disease, and the use of certain drugs should be considered (*table 1*). An idiopathic giant oesophageal ulcer can be diagnosed when no cause is established despite elaborate investigations.

Idiopathic giant oesophageal ulcers were initially reported in patients with acquired immunodeficiency syndrome (AIDS),[2] but were later also observed in other immunocompromised patients such as recipients of a solid organ transplant.[3-5] It has been described in an immunocompetent patient only once.[6] The pathogenesis of these ulcers, which are typically seen in the distal half of the oesophagus in the proximity of the gastro-oesophageal junction,[7] is not well understood.

In our patient, two episodes with an idiopathic giant oesophageal ulcer occurred and these both coincided with leucopoenia. To our knowledge, this concurrence has never been reported before, and we will discuss how this finding provides a novel insight into the development of the ulcer. Furthermore, we will argue the choice for treatment with steroids.

CASE

A 45-year-old man with end-stage renal disease due to IgA nephropathy underwent a pre-emptive transplantation with a kidney from a living related donor in November 2008.

Table 1. *Causes of oesophageal ulceration*

Gastro-oesophageal reflux disease
Infectious
• Virus: cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV)
• Bacterial: mycobacterium
• Fungi: candida, histoplasma
• Protozoa: leishmania
Neoplasms
• Carcinoma
• Lymphoma
• Kaposi sarcoma
Systemic disease
• Systemic lupus erythematosus
• Sarcoidosis
Medication
• Antibiotics: doxycycline, tetracycline, clindamycin
• Nonsteroidal anti-inflammatory drugs
• Bisphosphonates
• Remaining: potassium chloride, quinidine, mycophenolate mofetil

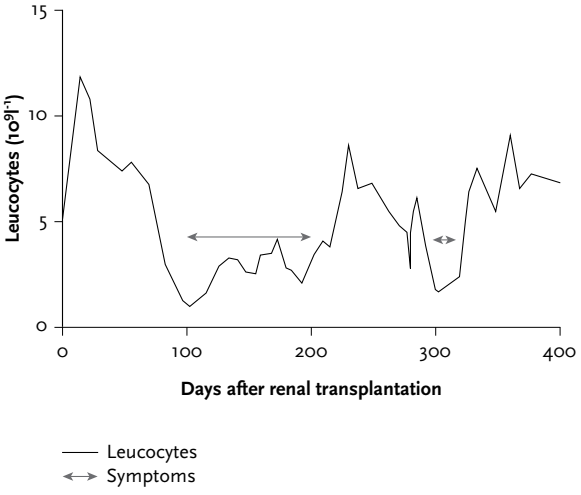
The immunosuppressive regimen consisted of tacrolimus, prednisone and mycophenolate mofetil (MMF). Furthermore, 700 mg of rituximab was administered as induction therapy during transplant surgery in the framework of a clinical trial (clinicaltrials.gov; NCT00565331). Since the donor was seropositive for cytomegalovirus (CMV) while the recipient was seronegative prior to transplantation, prophylactic therapy with valganciclovir was started postoperatively. The direct post-transplantation course was uncomplicated. In April 2009, the patient was admitted because of retrosternal discomfort for three weeks. The pain worsened during food intake. He reported weight loss of six kilograms, fatigue, but no night sweats or fever. Physical examination was unremarkable except for a decreased skin turgor.

At admission, the leucocytes were 2.8 x 10^9/l with 84% neutrophils, 9% lymphocytes, 3% monocytes and 4% (meta)myelocytes. Later on, the leucocytes decreased to 1.9 x 10^9/l with 70% neutrophils and 22% lymphocytes. Discontinuation of MMF and co-trimoxazole (prophylaxis for *Pneumocystis jirovecii*) did not have any beneficial effect. The other laboratory results were unremarkable. Upper gastrointestinal endoscopy revealed a cratered oesophageal ulcer covering 33% of the circumference (size 20 by 12 mm). Biopsy samples showed ulceration without any indication of the cause, the cultures were negative. Serological tests for human immunodeficiency virus, CMV, herpes simplex virus, histoplasma, and antinuclear antibodies were also negative. CMV polymerase chain reaction in blood and tissue was negative. PET-CT scan showed increased uptake of (18)F-2-fluoro-2-deoxy-D-glucose in the distal part of the oesophagus without signs of lymphadenopathy. Bone marrow biopsy revealed hypocellular bone marrow with reactive changes without signs of lymphoproliferative disease. Cytogenetic examination of the bone marrow was unremarkable. Endoscopic ultrasonography revealed thickening of all layers of the oesophageal wall (8.1 mm). Eventually, by exclusion, an idiopathic giant oesophageal ulcer was diagnosed. The patient was treated with prednisone 40 mg/day and the symptoms rapidly decreased and resolved within 72 hours. Repeated upper endoscopy after a few weeks showed a healing ulcer. The leucocytes also improved after increasing the dose of prednisone. Subsequently, the daily prednisone dose was tapered by 10 mg per month. The dose of tacrolimus was continued unchanged. Four months later, the patient was re-admitted because of *Pneumocystis jirovecii* pneumonia and he was successfully treated with co-trimoxazole. After discharge, leucopoenia and later on also new oesophageal ulcerations recurred. Elaborate investigations to settle the aetiology of the leucopoenia and ulcer were again unsuccessful. After increasing the prednisone dose, the leucopoenia and ulceration improved.

DISCUSSION

Idiopathic giant oesophageal ulcers are rarely seen and their pathogenesis is not well understood. In our patient, leucopoenia was present during both episodes of ulceration and the degree of leucopoenia was related to the severity of the ulceration (*figure 1*). Therefore, the leucopoenia might bear a relationship with the pathogenesis of the idiopathic giant oesophageal ulcer.

Figure 1. *Time course of white-cell counts in peripheral blood and symptoms. The period with symptoms of retrosternal discomfort is marked with arrows*



Initially, we were not able to clarify the cause of leucopoenia despite elaborate investigations and discontinuation of potentially myelotoxic drugs, except tacrolimus. However, our patient had also received rituximab at the time of transplantation, and it is known that leucopoenia can occur more than three weeks after the administration of rituximab.[8-11] Typically, it is characterised by profound neutropenia. As in our patient, lymphopenia and hypogammaglobulinemia were also observed.[11]

The aetiology of this so-called late-onset neutropenia is poorly understood and different hypotheses have been postulated. One of these hypotheses is that late-onset neutropenia after rituximab treatment is the consequence of an immune-mediated imbalance between various lymphocyte subpopulations.[10] Interestingly, an inverted CD4/CD8 ratio has been described in patients with late-onset neutropenia.[12]

Recently, treatment with rituximab has been associated with ulcerative lesions in the large bowel.[13] Histopathology showed infiltration with CD8 positive T lymphocytes. Identical histopathological findings were reported in AIDS-related idiopathic giant oesophageal ulcers.[14] Notably, in our patient a moderate infiltration of CD8 positive lymphocytes (*figure 2*) was present in the oesophageal biopsy specimen, which is usually not the case.[14] Thus, it appears that an imbalance between various lymphocyte subpopulations can be involved in the rituximab-induced neutropenia as well as in the pathogenesis of giant oesophageal ulcer.

In our patient, the relapse of oesophageal ulcer was accompanied by a recurrence of the leucopoenia, which supports a common pathogenetic basis. Recurrent episodes of neutropenia after rituximab, even without repeated administration of rituximab, have also been reported by others.[9]

Although oesophageal ulcers can regress after reduction of the tacrolimus dose,[3] we did not change the dose of tacrolimus in our patient. In line with literature data, we treated our patient successfully with corticosteroids.[2] In AIDS patients, endoscopically documented ulcer healing was observed in 85% of patients treated with steroids.[15] The mechanisms for steroid efficacy are unknown. In AIDS patients the relapse rate after discontinuing steroids is high (40%), but retreatment is usually successful.[4] In case of refractory ulcers, thalidomide has also been used successfully.[6]

In conclusion, the perioperative administration of rituximab was the likely cause of the relapsing leucopoenia and the coinciding idiopathic giant oesophageal ulcer in our patient.

ACKNOWLEDGMENTS

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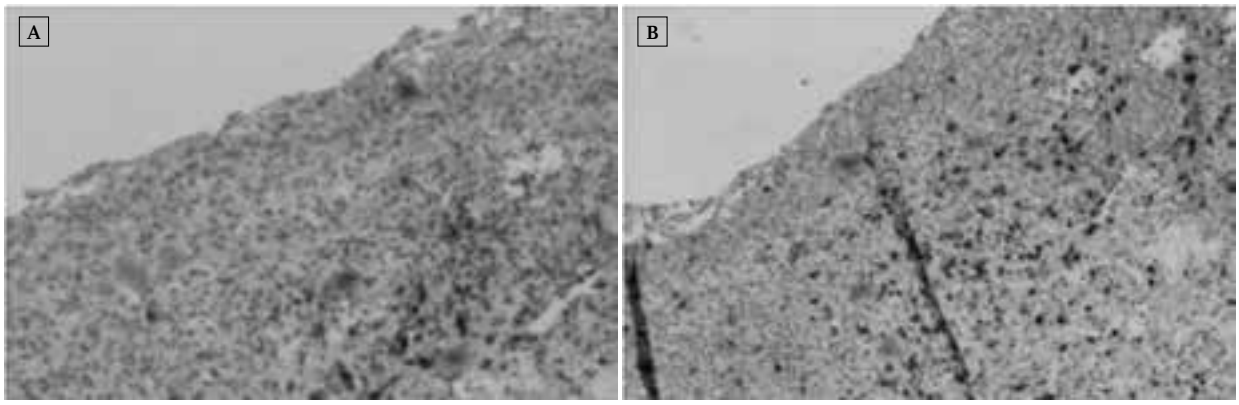
REFERENCES

1. Ponticelli C, Passerini P. Gastrointestinal complications in renal transplant recipients. Transpl Int. 2005;18:643-50.
2. Wilcox CM, Schwartz DA, Clark WS. Esophageal ulceration in human immunodeficiency virus infection. Causes, response to therapy, and long-term outcome. Ann Intern Med. 1995;123:143-9.
3. Dang S, Atiq M, Krishna S, Lamps LW, Olden KW, Aduli F. Idiopathic esophageal ulcers after autologous hemopoetic stem cell transplant: possible role of IgA levels. Ann Hematol. 2008;87:1031-2.
4. Farrell JJ, Cosimi AB, Chung RT. Idiopathic giant esophageal ulcers in a renal transplant patient responsive to steroid therapy. Transplantation. 2000;70:230-2.

Figure 2. *Immunohistochemical characterisation of the inflammatory giant oesophageal infiltrate by CD 4 (left) and CD 8 (right). The estimated ratio CD4/CD8 is 1.0 in this representative sample*



5. Atiq M, Neff GW, Argyropoulos C, et al. Successful treatment with thalidomide in a liver transplant recipient with giant esophageal ulcers. Liver Transpl. 2006;12:987-8.

6. Ollivier S, Bonnet J, Lemann M, et al. Idiopathic giant oesophageal ulcer in an immunocompetent patient. The efficacy of thalidomide treatment. Gut. 1999;45:463-4.

7. Bach MC, Valenti AJ, Howell DA, Smith TJ. Odynophagia from aphthous ulcers of the pharynx and esophagus in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med. 1988;109:338-9.

8. Dunleavy K, Tay K, Wilson WH. Rituximab-associated neutropenia. Semin Hematol. 2010;47:180-6.

9. Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine (Baltimore). 2010;89:308-18.

10. Papadaki T, Stamatopoulos K, Anagnostopoulos A, Fassas A. Rituximab-associated immune myelopathy. Blood. 2003;102:1557-8.

11. Chaiwatanatorn K, Lee N, Grigg A, Filshie R, Firkin F. Delayed-onset neutropenia associated with rituximab therapy. Br J Haematol. 2003;121:913-8.

12. Stamatopoulos K, Papadaki T, Pontikoglou C, et al. Lymphocyte subpopulation imbalances, bone marrow hematopoiesis and histopathology in rituximab-treated lymphoma patients with late-onset neutropenia. Leukemia. 2008;22:1446-9.

13. Ardelean DS, Gonska T, Wires S, et al. Severe ulcerative colitis after rituximab therapy. Pediatrics. 2010;126:e243-6.

14. Siegmund B, Moos V, Loddenkemper C, et al. Esophageal giant ulcer in primary human immunodeficiency virus infection is associated with an infiltration of activated T cells. Scand J Gastroenterol. 2007;42:890-5.

15. Adeoti AG, Vega KJ, Dajani EZ, Trotman BW, Kloser PC. Idiopathic esophageal ulceration in acquired immunodeficiency syndrome: successful treatment with misoprostol and viscous lidocaine. Am J Gastroenterol. 1998;93:2069-74.

Netherlands
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PHOTO QUIZ

A pubic mass

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CASE REPORT

A 71-year-old woman, receiving palliative treatment for pancreatic carcinoma, presented with pain in her right leg. Her medical history included diabetes type 2, hypertension, aortic bifurcation graft surgery in 2005, a femoro-femoral crossover graft in 2007 and metastatic pancreatic carcinoma since 2006.

She had been complaining about pain in her upper right leg for several months, which worsened by movement. The patient related the pain to a swelling on her lower abdomen. The swelling had been there for a couple of years and was of unknown cause.

Physical examination showed two adjacent round lumps of about 7 x 7 cm at her pubic bone. The mass was painless, had a firm consistency and was nonpulsatile (*figure 1*). A computed tomography (CT) scan of the abdomen showed a large collection of fluid in front of the pubic bone with contrast in the centre (*figure 2*).

Figure 1.

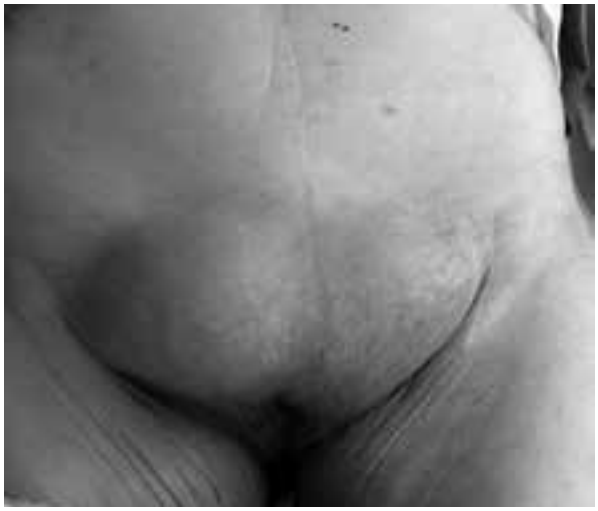
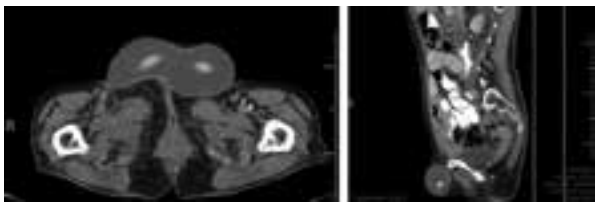


Figure 2.



WHAT IS YOUR DIAGNOSIS?

See page 378 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

A worm emerging from the foot

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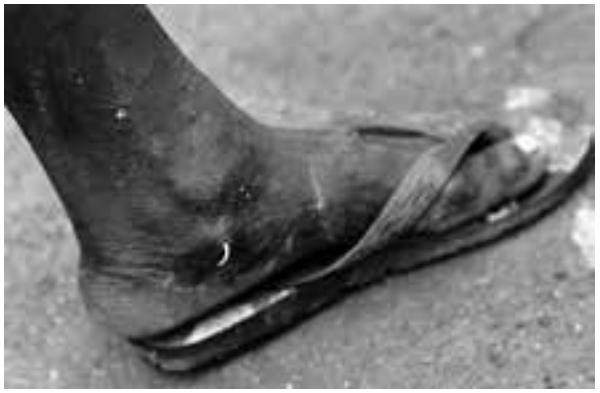
CASE REPORT

A 34-year-old man presented to a Sudanese clinic with a one-week history of a hot, painful sensation under the skin of the medial side of his left ankle. Three days before, he had noticed a small, painful blister under the medial malleolus. Since then, there was increasing swelling and pruritus around the blister. In addition, he had developed a slight fever with dizziness and nausea. On physical examination, it was noted that the blister had burst and a worm was emerging (*figure 1*).

Figure 1. *Guinea worm emerging from the foot (photo by Dr. A. Tayeh)*



WHAT IS YOUR DIAGNOSIS?

See page 379 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

A spangled colon

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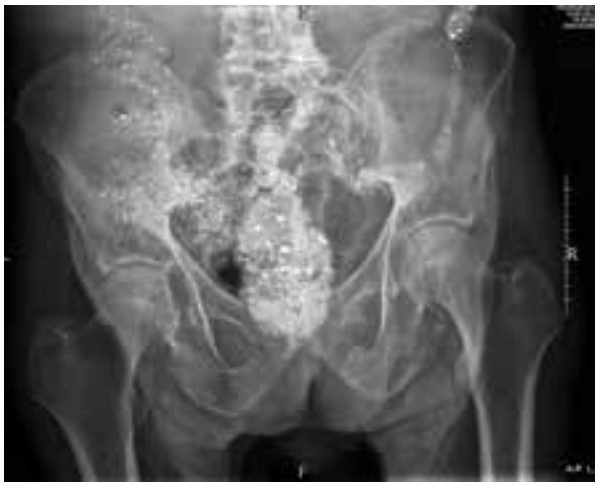
CASE REPORT

A 85-year-old male patient receiving chronic haemodialysis treatment presented with weight loss and multiple ulcers on his upper and lower extremities without preceding trauma. His medical history included right-sided hemicolectomy for colon carcinoma, prostate carcinoma, and recently a fracture of his left olecranon. Arterial duplex imaging of the lower extremities revealed no significant macrovascular disease. Because calciphylaxia was considered in the differential diagnosis, a series of plain X-ray images of the pelvis and lower extremities was performed to screen for extravascular calcifications. While the latter showed no pathology, the X-ray of the pelvis showed the following picture *(figure 1)*.

Figure 1. *Plain X-ray image of the pelvis showing numerous opacifications*



WHAT IS YOUR DIAGNOSIS?

See page 380 for the answer to this photo quiz.

PHOTO QUIZ

A female with a leiomyosarcoma presenting with acute thoracic pain and dyspnoea

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CASE REPORT

A 49-year-old female was admitted to the Medical Oncology ward because of acute pain in her right lower chest. Seven days before she had started the first course of dacarbazine because of leiomyosarcoma of the uterus with pulmonary and pleural metastases. On admission a chest X-ray was performed, which is shown in *figure 1*. We started low-dose intravenous morphine and the pain subsided. However, eight hours later she woke up with acute dyspnoea, followed by loss of consciousness. The chest X-ray at that time is depicted in *figure 2*.

WHAT IS YOUR DIAGNOSIS?

See page 380 for the answer to this photo quiz.

Figure 1. *X-thorax (AP) taken on admission*

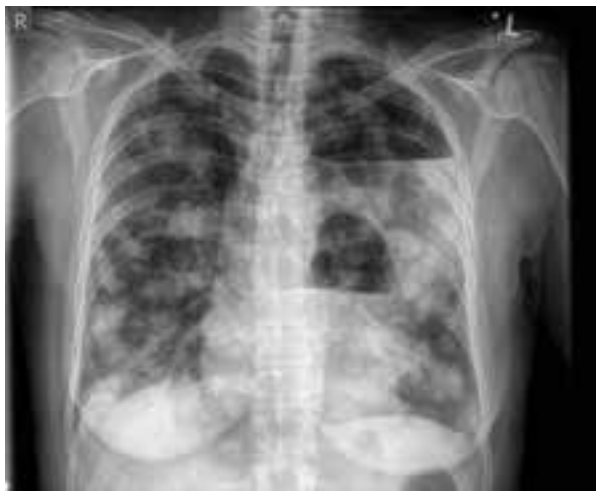
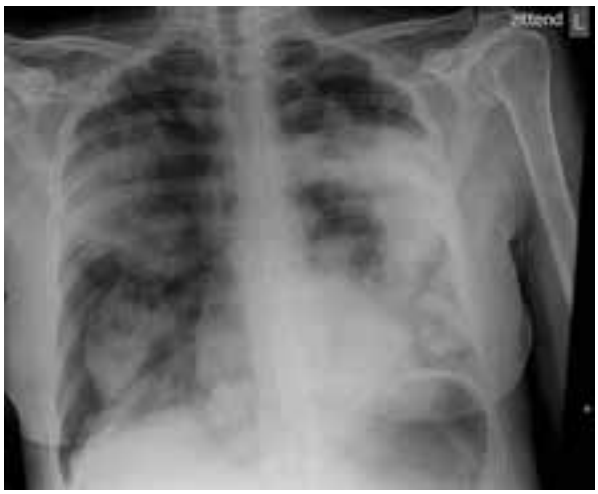


Figure 2. *X-thorax during acute dyspnoea and loss of consciousness*



ANSWER TO PHOTO QUIZ (PAGE 374)

A PUBIC MASS

DIAGNOSIS

The mass consisted of a fluid collection around the femoro-femoral crossover, which had been placed in 2007. The crossover was still functional.

Multiple cases of periprosthetic fluid collection have been described, mostly with an aortic prosthesis. In these patients a fluid collection will not be noticed except in case of secondary infection. However, the graft in our patient was localised close to the skin and the fluid collection was clearly visible.

Perigraft haematomas shortly after surgery are a common phenomenon of an aortic graft, with reports of up to 90%, which in most cases resolve over time.[1]

Perigraft seromas, which can appear even months after surgery, are rarely recognised, but exist in 18-50% of patients.[2,3] Influencing factors are diabetes, smoking and anticoagulation therapy. The pathophysiology is not well understood. It could be caused by an immunoallergic reaction to the graft or due to modification of the permeability of the prosthetic wall.

The clinical course of these fluid collections is variable: some resolve, others are stable and some enlarge.[2]

In case of infection of the fluid collection, intervention is needed. It seems that drainage is not enough to relieve symptoms and replacing the graft is the treatment of choice.[2]

Our patient had diabetes as a risk factor for a perigraft seroma. As her pancreatic cancer was progressive we decided not to perform a surgical intervention.

REFERENCES

1. Spartera C, Morettini G, Petrassi C, et al. Role of magnetic resonance imaging in the evaluation of aortic graft healing, perigraft fluid collection, and graft infection. Eur J Vasc Surg. 1990;4:69-73.
2. Hurie J, Patel HJ, Criado E, et al. Postoperative fluid collection after hybrid debranching and endovascular repair of thoracoabdominal aortic aneurysms. J Vas Surg. 2011;54:1623-8.
3. Kadakol AK, Nypaver TJ, Lin JC, et al. Frequency, risk factors, and management of perigraft seroma after open abdominal aortic aneurysm repair. J Vasc Surg. 2011;54:637-43.

ANSWER TO PHOTO QUIZ (PAGE 375)

A WORM EMERGING FROM THE FOOT

DIAGNOSIS

This classical finding prompted the diagnosis of dracunculiasis, or 'Guinea worm disease'.

Dracunculiasis is an entirely preventable tropical waterborne parasitic disease caused by the nematode *Dracunculiasis medinensis*. It is transmitted by the ingestion of water contaminated with copepods (water fleas) that are infected with larvae of the worm. In the stomach, the larvae penetrate through the digestive wall. While the male worms die within months, the females may grow up to 1 meter (3 feet) in length.[1] Symptoms start approximately one year after the initial infection when a worm emerges from the skin. Immersing the affected limbs in water creates the opportunity for the worm to expel millions of larvae. These are ingested by copepods and the cycle starts all over again. The social impact of dracunculiasis is mainly due to the temporary disability it causes among patients. In endemic areas, the disease is a considerable public health problem. It affects the poorest populations, often living in rural and inaccessible areas. Since the disease mainly affects the most productive people, it has significant impact on agricultural productivity and school attendance.[2] However, over the past decades, enormous progress has been made towards the global eradication of the disease and the overall number of cases has been reduced by more than 99% since 1986.[3]

The patient was treated by gradually pulling the worm out manually, winding it up onto a stick a few inches each day for seven weeks. During this period, the foot was bandaged daily. Although this does not prevent the release of larvae, it does discourage the patient from immersing his foot in water that is also used by others.[4] In addition, topical antibiotics were applied to the wound to prevent secondary bacterial infections.

REFERENCES

1. Greenaway C. Dracunculiasis (guinea worm disease). CMAJ. 2004;170:495-500.
2. Visser BJ. Dracunculiasis eradication – Finishing the job before surprises arise. Asian Pac J Trop Med. 2012;5:505-10.
3. Cairncross S, Tayeh A, Korkor AS. Why is dracunculiasis eradication taking so long? Trends Parasitol. 2012;28:225-30.
4. Cairncross S, Muller R, Zagaria N. Dracunculiasis (Guinea Worm Disease) Eradication Initiative. Clin Microbiol Rev. 2002;15:223-46.

ANSWER TO PHOTO QUIZ (PAGE 376)

A SPANGLED COLON

DIAGNOSIS

The X-ray image showed multiple opacifications located in the distal digestive tract (colon). The opacifications were caused by the presence of the drug lanthanum carbonate, a phosphate binder commonly used in dialysis patients. The X-ray finding is normal in patients who use this drug and has no clinical importance.
Lanthanum carbonate is a nonaluminium, noncalcium phosphate-binding agent. The element lanthanum has 57 protons, one more than the metallic alkaline earth element barium.

Several other substances may cause a more or less comparable picture, including barium enema and the drug bismuth citrate.[1] Our patient had not used any of these agents, nor had he undergone any procedure requiring the use of contrast media.

The suspected diagnosis calciphylaxia was not confirmed. The patient died two weeks later with the clinical picture of refractory cachexia.

Lanthanum carbonate is a commonly used drug in patients with advanced renal insufficiency. Considering the increasing number of these patients, it may be expected that the radiographic 'abnormality' described here will be increasingly encountered in the near future. Knowledge of the cause of these opacifications will prevent unnecessary diagnostic work-up.

REFERENCES

1. Chan YC, Lau FL, Chan JCS, Hon TYW. A study of drug radiopacity by plain radiography. Hong Kong J Emerg Med. 2004;11:205-10.

ANSWER TO PHOTO QUIZ (PAGE 377)

A FEMALE WITH A LEIOMYOSARCOMA PRESENTING WITH ACUTE THORACIC PAIN AND DYSPNOEA

DIAGNOSIS

The repeated thoracic X-rays showed rapidly progressive pneumothorax and hydropneumothorax in a patient known with pulmonary and pleural metastases of a uterine leiomyosarcoma. *Figure 1* shows left-sided hydropneumothorax with air-fluid level apical, cavitating intrapulmonal lesion paravertebral in the lingual lobe of the left lung with air-fluid level and multiple bilateral densities. *Figure 2* shows bilateral pneumothorax with partially collapsed lung due to pleural adhesions in lung with known multiple intrapulmonal densities. Spontaneous pneumothorax in leiomyosarcomas of the uterus has been reported previously,[1] but this extremely rapid progression is rarely observed. Possible causes of leiomyosarcoma-associated pneumothorax are the formation of bronchopleural fistulae secondary to tumour invasion or necrosis, direct pleural invasion by the tumour or a 'check valve' mechanism.[1] In this last case the small airways are narrowed by cancer invasion, leading to the entrapment of air in and eventually rupture of alveolar spaces.
Because of the very rapid clinical deterioration of our patient and dismal prognosis we refrained from further interventions. Intravenous morphine was administered and she died within 45 minutes after the second X-ray was taken.

REFERENCES

1. Srinivas S, Varadhachary G. Spontaneous pneumothorax in malignancy: a case report and review of the literature. Ann Oncol. 2000;11:887-9.

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SPECIAL REPORT

The 2012 revised Dutch national guidelines for the treatment of chronic hepatitis B virus infection

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ABSTRACT

In 2008, the Netherlands Association of Gastroenterologists and Hepatologists (Nederlands Vereniging van Maag-Darm-Leverartsen) published the Dutch national guidelines for the treatment of chronic hepatitis B virus infection. New insights into the treatment of chronic hepatitis B with relevance for clinical practice have been adopted in these concise, revised guidelines. The most important changes include the choice of initial antiviral therapy, licensing of tenofovir for the treatment of chronic hepatitis B and the management of antiviral resistance.

KEYWORDS

Hepatitis B virus, guidelines, antiviral therapy, pregnancy

CHOICE OF ANTIVIRAL THERAPY

In May 2010, the European Medicines Agency (EMA) changed the licence of lamivudine; lamivudine is no longer recommended as first-line therapy for the treatment of chronic hepatitis B if other (newer) antiviral agents are available and reimbursed. Since treatment with adefovir and telbivudine also results in a higher risk of antiviral resistance compared with entecavir and tenofovir,[1,2] these drugs are no longer recommended as first-line therapy. Pegylated interferon (PEG-IFN), entecavir and tenofovir are now the preferred first-line drugs for the treatment of chronic hepatitis B.

Recommendation

Level 2	PEG-IFN, entecavir and tenofovir should be considered as first-line therapy for chronic hepatitis B. Lamivudine, adefovir and telbivudine are no longer drugs of choice because of the higher risk of antiviral resistance compared with entecavir and tenofovir.

TENOFOVIR FOR THE TREATMENT OF CHRONIC HEPATITIS B

Shortly after the publication of the 2008 guidelines, tenofovir was licensed for the treatment of chronic hepatitis B virus infection. The drug has been used for the treatment of HIV since 2002. As in HIV, tenofovir is administered as tenofovir disoproxil fumarate in a dosage of 245 mg once daily.

The efficacy of tenofovir was evaluated in two randomised controlled trials in which patients received either tenofovir or adefovir.[3,4] These trials showed that in both HBeAg-positive and HBeAg-negative patients tenofovir was superior to adefovir; viral suppression was more profound, alanine aminotransferase (ALAT) normalisation rates were higher and HBsAg loss occurred more often in tenofovir-treated patients. In HBeAg-positive patients, one year of tenofovir therapy resulted in HBeAg seroconversion in 21% of patients and serum HBV DNA below 80 IU/ml (400 copies/ml) in 76% of patients.[4] After three years of continuous tenofovir therapy, the proportion of patients with undetectable HBV DNA and negative HBeAg increased to 93% and 34%, respectively.[5] ALAT normalisation was observed in 68% of patients after one year and increased to 74% after three years of therapy.[4,5] The proportion of patients with clearance of HBsAg also increased with increasing duration of therapy to 8% and 10% after three and four years of tenofovir therapy, respectively.[5,6] In HBeAg-negative patients, HBV DNA levels below 80 IU/ml (400 copies/ml) were observed in 93% of patients after one year, with normalisation of ALAT in 76% of patients. After three years, these rates were 99% and 81%.[5]

In patients with insufficient decline of HBV DNA during treatment with lamivudine or adefovir (HBV DNA >2.0 x 10^3 IU/ml [>1.0 x 10^4 copies/ml]) after at least six months of therapy, treatment with tenofovir resulted in serum HBV DNA below 80 IU/ml (400 copies/ml) in 79% of patients after a mean treatment duration of two years.[7] Presence of lamivudine-resistant strains did not influence response to tenofovir. However, presence of mutations associated with adefovir resistance resulted in serum HBV DNA below 80 IU/ml (400 copies/ml) in about 50% of patients without evidence of mutations associated with tenofovir resistance.[7] No mutations associated with tenofovir resistance have been identified so far.

TENOFOVIR AND RENAL INSUFFICIENCY

The interval of tenofovir administration should be increased in patients with renal insufficiency (creatinine clearance <50 ml/min). For patients with a creatinine clearance of 30-49 ml/min the recommended dosage interval is 48 hours. For patients with a creatinine clearance <30 ml/min the European Medicines Agency (EMA) recommends to use another antiviral agent when possible. If there is no possibility for treatment with another antiviral agent with expected comparable efficacy, the recommended dosage interval for tenofovir is every 72 to 96 hours in case of a creatinine clearance of 10-29 ml/min. In haemodialysis patients, tenofovir should be administered once weekly after dialysis.

Renal toxicity has been observed in patients receiving tenofovir. Progressive renal proximal tubular dysfunction with loss of phosphate, proteinuria, loss of amino acids and glucosuria has been described. Mild to moderate proximal tubular dysfunction was found in 22-53% of HIV-infected patients treated with tenofovir.[8,9] The Fanconi syndrome is caused by this proximal tubular dysfunction and can result in a diminished glomerular filtration rate. In severe cases the associated loss of phosphate can result in osteomalacy. Increase in serum creatinine levels and hypophosphataemia generally occurs late in the course of the renal disease. More sensitive markers for the early detection of tubular dysfunction are normoglycaemic glucosuria, hyperalbuminuria, hyper β2-microglobulinuria and the renal tubular reabsorption of phosphate (TmP-GFR).[8,9] Tenofovir-associated proximal tubular dysfunction has not (yet) been well studied in HBV-infected patients.

If tenofovir therapy is considered in a patient with renal insufficiency, the following aspects should be carefully weighted: the indication for antiviral therapy, the potential benefits and adverse events of tenofovir therapy, as well as alternative treatment options.

NEW INSIGHTS FOR ENTECAVIR AND PEGINTERFERON (PEG-IFN)

For entecavir and PEG-IFN the results of new studies with a longer duration of follow-up have become available. After five years of continuous treatment with entecavir serum HBV DNA was below 60 IU/ml (300 copies/ml) in 94% of patients. Antiviral resistance was found in 1.2% of these patients.[10]

After a mean period of three years, 81% patients with an initial response to PEG-IFN (HBeAg negative at six-months post-treatment) were still HBeAg negative and 30% of these patients had cleared serum HBsAg (with an overall HBsAg clearance rate of 11%).[11] Shortening of the treatment duration of peginterferon from 12 months to six resulted in lower response rates,[12] as did lowering the weekly dosage to 90 μg (compared with the standard 180 μg).

Recent studies have provided data which can be helpful in estimating the chance of response prior to starting PEG-IFN therapy and for the early prediction of

non-response during therapy. A model for the prediction of response to PEG-IFN therapy has been developed for HBeAg-positive patients (see also www.liver-gi.nl/peg-ifn).[13] The best candidates for PEG-IFN are those with HBV genotype A and high ALAT (>2 times the upper limit of normal) or HBV DNA <2.0 x 10^8 IU/ml (<1.0 x 10^9 copies/ml). The same applies for HBV genotype B or C infected patients with both high ALAT levels and HBV DNA <2.0 x 10^8 IU/ml (<1.0 x 10^9 copies/ml).[13]

Quantitative measurement of serum HBsAg is useful for the early prediction of non-response to PEG-IFN. There was virtually no chance of response in HBeAg-negative patients who had no decline of serum HBsAg and a less than 2$\log_{10}$ decline in HBV DNA after 12 weeks of PEG-IFN therapy. Discontinuation of therapy should therefore be considered in these patients.[14,15] Serum HBsAg levels after 12 weeks of peginterferon therapy also seem to be associated with a chance of response in HBeAg-positive patients. However, no firm recommendations can be provided for HBeAg-positive patients at this moment.[16]

FOLLOW-UP OF ANTIVIRAL THERAPY

Treatment with nucleos(t)ide analogues is generally well tolerated. Severe adverse events have been described in a small proportion of patients. As mentioned above, cases of Fanconi syndrome, renal insufficiency and osteomalacy have been observed in patients treated with adefovir and tenofovir.[17,18] It is therefore recommended to monitor serum creatinine and phosphate levels every three months in tenofovir-treated patients (also see above). Lactate acidosis was previously described in HIV-infected patients treated with nucleos(t)ide analogues and has also been observed in HBV-infected patients with decompensated cirrhosis during entecavir therapy.[19] It is therefore recommended to monitor lactate levels in patients with (decompensated) cirrhosis who are treated with nucleos(t)ide analogues. The revised recommendations for monitoring antiviral therapy are shown in *table 1*.

Because of the very low risk of antiviral resistance in patients treated with entecavir or tenofovir, HBV DNA does not need to be measured every three months after the first year of therapy. Measurement of HBV DNA every 6-12 months seems sufficient in these patients. With increasing duration of therapy, increasing rates of undetectable HBV DNA have been observed in tenofovir and entecavir treated patients (without pre-existing lamivudine resistance).[10,20] Currently available data suggest that there is no increased risk of antiviral resistance in patients who show a slow but gradual decline in HBV DNA during treatment with these antiviral agents. Therefore, there is no need for more frequent measurement of HBV DNA or a change in antiviral therapy.

Antiviral therapy can possibly be discontinued in patients who have confirmed HBeAg seroconversion during treatment with nucleos(t)ide analogues (at least a six-month interval between two tests). However, a recent study showed that about half of patients had reversion to detectable HBeAg after stopping nucleos(t)ide analogue therapy.[21] It may therefore be better to only stop nucleos(t)ide analogue therapy in case of HBsAg loss.

Recommendation

Level 4	It is recommended to perform quantitative measurement of HBV DNA every three months during the first year of therapy. Measurement every six to 12 months suffices thereafter.
Level 2	There is no need to change to antiviral therapy in patients with persistently detectable, but declining HBV DNA levels during treatment with entecavir or tenofovir. For entecavir-treated patients this does not apply to those with previous lamivudine therapy.

Table 1. *Recommendations on minimal laboratory testing during antiviral therapy with peginterferon (PEG-IFN) or nucleos(t)ide analogues (entecavir or tenofovir)*

	Start of therapy	PEG-IFN	Nucleos(t)ide analogues year 1	Nucleos(t)ide analogues after year 1
Aminotransferases (ASAT, ALAT)	Once	4-weekly[1]	3-monthly	6-12 monthly
Liver function (bilirubin, albumin, prothrombin time)	Once	3-monthly	3-monthly	6-12 monthly
Kidney function (creatinine,[2] phosphate[3])	Once	3-monthly	3-monthly	3-monthly
Lactate			3-monthly[4]	3-monthly[4]
Blood count (platelets, neutrophil count)	Once	4-weekly		
Endocrinology (TSH)	Once	3-monthly		
Virus serology (HBsAg,[5] anti-HBs,[5] HBeAg, anti-HBe, HBV genotype is recommended if PEG-IFN therapy is considered)	Once	3-monthly	3-6 monthly	6-12 monthly
Quantitative HBV DNA	Once	3-6 monthly	3-6 monthly	6-12 monthly

[1]Also after 2 weeks of therapy; [2]assessment of 24-hour creatinine clearance is recommended in patients with elevated creatinine; [3]only for tenofovir; [4]only for patients with cirrhosis; [5]HBsAg and anti-HBs only after HBeAg seroconversion or repeatedly undetectable HBV DNA (HBV DNA <80 IU/ml [<400 copies/ml])

ANTIVIRAL RESISTANCE

The recommendations on antiviral resistance have also been revised. Lamivudine, adefovir and telbivudine may be unsafe in patients with severe fibrosis or cirrhosis (Metavir 3-4 or comparable in other fibrosis scoring systems) due to the high risk of antiviral resistance. These patients are at risk of developing decompensated liver disease in case of viral breakthrough with subsequent hepatitis flares. Antiviral resistance can even occur after several years of profound viral suppression. Therefore, changing antiviral therapy to entecavir or tenofovir is recommended in these patients, even if there are no signs of antiviral resistance. In all other lamivudine, adefovir and telbivudine treated patients switching to entecavir or tenofovir can be considered.

Treatment recommendations for patients with documented antiviral resistance are shown in *table 2*. It has been shown that adding adefovir to lamivudine was superior to switching to adefovir in patients with lamivudine resistance.[22] However, there is no evidence that add-on therapy with entecavir or tenofovir is more effective in case of lamivudine or adefovir resistance.[7,23,24] Adding entecavir or tenofovir to ongoing treatment with another antiviral agent is therefore not recommended. Since there are no known mutations in the HBV polymerase that result in tenofovir resistance, genotypical analysis is currently not recommended for tenofovir-treated patients..

Recommendation

Level 4	Changing antiviral therapy to entecavir or tenofovir is recommended in lamivudine, adefovir and telbivudine treated patients with severe fibrosis or cirrhosis, even if there are no signs of antiviral resistance. Changing antiviral therapy can be considered in all other patients receiving lamivudine, adefovir and telbivudine.

Tabel 2. *Recommended antiviral drugs in case of antiviral resistance*

Type of antiviral resistance	Recommended treatment option
Lamivudine resistance	Switch to tenofovir
Adefovir resistance	Switch to entecavir (switch to tenofovir)
Entecavir resistance	Switch to tenofovir
Telbivudine resistance	Switch to tenofovir

Controlled studies are often not available. Treatment options between brackets are not preferred.

PREGNANCY AND HEPATITIS B

Several factors have to be considered in women with chronic hepatitis B virus infection who are trying to conceive. These include the potential adverse events and benefits of postponing antiviral therapy, continuing antiviral therapy during pregnancy and delaying pregnancy until after the completion of antiviral therapy (with PEG-IFN).

Tenofovir has pregnancy classification B and there is already quite some experience with tenofovir during pregnancy in HIV-infected women. Treatment with tenofovir can therefore be considered in the third trimester of pregnancy (from week 32) in patients with HBV DNA >2.0 x 10^8 IU/ml (>1.0 x 10^9 copies/ml). In such patients, additional treatment with lamivudine, which has pregnancy classification C, results in a significantly lower chance of HBV infection in the newborn baby compared with stand-alone passive-active immunisation.[25,26] Continuation of tenofovir or lamivudine after delivery is recommended if there is also an indication for antiviral therapy for the mother (based on viral load, hepatitis and/or liver fibrosis). Antiviral therapy can be stopped three months after delivery in all other patients. Monitoring of transaminase levels is recommended because an increase in hepatitis activity can occur. ALAT elevations were observed in more than half of pregnant women who discontinued lamivudine after delivery. This seemed to occur particularly in those with elevated ALAT at the start of lamivudine therapy.[27] Because of the lower risk of antiviral resistance, tenofovir is preferred over lamivudine if a prolonged course of antiviral treatment is expected. In women who become pregnant during antiviral therapy, the risk of increased hepatic inflammation after stopping antiviral therapy should be balanced against the risk of teratogenicity. Congenital abnormalities were found in 2.6% of about 9000 registered pregnancies during treatment with lamivudine. For tenofovir this rate was 2.2% in nearly 1400 pregnancies.[26] These rates are comparable with those observed in a matched control group. No recommendations can be made about breast feeding during treatment with lamivudine and tenofovir since data are lacking. It is known that both drugs are excreted in breast milk.

At this moment no firm recommendations can be made about *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) for HBV carriers; data are mostly limited to *in vitro* findings.[28] Appropriate semen storage is no longer an issue nowadays and is crucial for male HBV carriers. Based on the available data, IVF seems safe in both male and female HBV carriers. ICSI seems safe for male HBV carriers when standard semen washing procedures are applied. Integration of HBV DNA in the genome of the embryo might occur in female HBV carriers. However, HBV DNA was not detected after accidental exposure of embryos to HBV.[28]

REFERENCES

1. Liaw YF, Gane E, Leung N, et al. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology. 2009;136:486-95.
2. Marcellin P, Chang TT, Lim SG, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. Hepatology. 2008;48:750-8.
3. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology. 2010;140:132-43.
4. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359:2442-55.
5. Heathcote EJ, Marcellin P, Buti M, et al. Three-Year Efficacy and Safety of Tenofovir Disoproxil Fumarate Treatment for Chronic Hepatitis B. Gastroenterology. 2010:DOI 10.1053/j.gastro.2010.10.011.
6. Heathcote EJ, Gane E, De Man RA, et al. Long term (4 year) efficacy and safety of tenofovir disoproxil fumarate (TDF) treatment in HBeAg-positive patients (HBeAg+) with chronic hepatitis B (study 103): preliminary analysis. Hepatology. 2010;52:556A.
7. van Bommel F, de Man RA, Wedemeyer H, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology. 2010;51:73-80.
8. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. AIDS Res Hum Retroviruses. 2009;25:387-94.
9. Labarga P, Barreiro P, Martin-Carbonero L, et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. Aids. 2009;23:689-96.
10. Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology. 2010;51:422-30.
11. Buster EH, Flink HJ, Cakaloglu Y, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg positive patients treated with peginterferon alpha-2b. Gastroenterology. 2008;135:459-67.
12. Liaw YF, Xie Q, Han KB, et al. Shorter duration and lower dose of peginterferon alfa-2a therapy results in inferior HBeAg seroconversion rates compared with the duration and dose of 48 weeks and 180 μg: NEPTUNE study. Hepatology. 2010;52:429A-430A.
13. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. Gastroenterology. 2009;137:2002-9.
14. Rijckborst V, Hansen BE, Cakaloglu Y, et al. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. Hepatology. 2010;52:454-61.
15. Rijckborst V, Hansen BE, Ferenci P, et al. Early on-treatment HBsAg and HBV DNA levels identify HBeAg-negative patients not responding to 48 or 96 week of peginterferon alfa-2a therapy. Hepatology. 2010;52:552A-553A.
16. Sonneveld MJ, Rijckborst V, Boucher CA, Hansen BE, Janssen HL. Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. Hepatology. 2010;52:1251-7.
17. Jung YK, Yeon JE, Choi JH, et al. Fanconi's Syndrome Associated with Prolonged Adefovir Dipivoxil Therapy in a Hepatitis B Virus Patient. Gut Liver. 2010;4:389-93.
18. Verhelst D, Monge M, Meynard JL, et al Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis. 2002;40:1331-3.
19. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology. 2009;50:2001-6.
20. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology. 2011;140:132-43.
21. Reijnders JG, Perquin MJ, Zhang N, Hansen BE, Janssen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. Gastroenterology. 2009;139:491-8.
22. Lampertico P, Vigano M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology. 2007;133:1445-51.
23. Reijnders JG, Deterding K, Petersen J, et al. Antiviral effect of entecavir in chronic hepatitis B: influence of prior exposure to nucleos(t)ide analogues. J Hepatol. 2009;52:493-500.
24. Reijnders JG, Pas SD, Schutten M, de Man RA, Janssen HL. Entecavir shows limited efficacy in HBeAg-positive hepatitis B patients with a partial virologic response to adefovir therapy. J Hepatol. 2009;50:674-83.
25. Xu WM, Cui YT, Wang L, Yang H, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat. 2009;16:94-103.
26. Bzowej NH. Hepatitis B Therapy in Pregnancy. Curr Hepat Rep. 2010;9:197-204.
27. ter Borg MJ, Leemans WF, de Man RA, Janssen HL. Exacerbation of chronic hepatitis B infection after delivery. J Viral Hepat. 2008;15:37-41.
28. Lutgens SP, Nelissen EC, van Loo IH, Koek GH, Derhaag JG, Dunselman GA. To do or not to do: IVF and ICSI in chronic hepatitis B virus carriers. Hum Reprod. 2009;24:2676-8.

LETTER TO THE EDITOR

Bradykinin-receptor antagonist icatibant: possible treatment for ACE inhibitor-related angio-oedema

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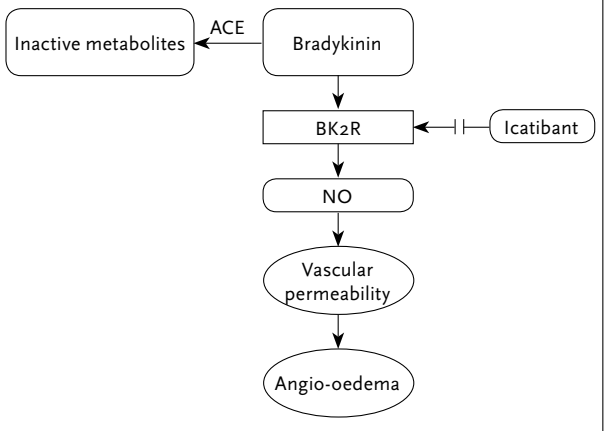
Dear Editor,

We would like to increase awareness of a new and potentially life-saving treatment option in angiotensin-converting enzyme (ACE) inhibitor-related angio-oedema. This condition can appear at any time during treatment with ACE inhibitors[1] and may present as life-threatening oropharyngeal oedema, which sometimes necessitates endotracheal intubation and observation in intensive care (ICU). As the angio-oedema is bradykinin and not histamine mediated (*figure 1*), the widely used treatment with prednisone and antihistamines is ineffective.[1,2] Therefore, the duration of oedema depends on the half-life time of the drug, among other things.

Figure 1. *Role of angiotensinconverting enzyme (ACE) in the pathofysiology of angio-oedema*



BK2R = bradykinin receptor type 2, NO = nitric oxide

Recently icatibant, a bradykinin receptor type 2 antagonist, was introduced as treatment for C1-esterase inhibitor deficiency (hereditary angio-oedema), which is also bradykinin mediated.[3,4] Since then, a small number of case reports and case series on the effects of icatibant in ACE inhibitor-related angio-oedema have been published, showing rapid reduction of oedema and prevention of the need for intubation.[5-7] Based on these positive results, we recently treated a 45-year-old woman who presented to our emergency department with progressive swelling of the tongue for several hours with icatibant. Medication use consisted of chlorthalidone, metoprolol, methotrexate, omeprazole, simvastatin, and lisinopril, the dose of which was recently raised from 10 to 20 mg daily. Before presentation, she had already been repeatedly treated, without response, with adrenaline 0.5 mg intramuscularly (IM), DAF (Di-Adreson-F) 25 mg intravenously and clemastine 0.5 mg IM. After admission, subcutaneous icatibant 30 mg was administered. Within a few minutes, the swelling of the tongue decreased and she was able to speak and articulate more clearly. There was no need for intubation. The total duration of hospital stay was two days.

Another patient who recently presented to the emergency department with swollen tongue and gums while being treated with fosinopril (since 2009) was not treated with icatibant and had to be admitted to the ICU for endotracheal intubation for 24 hours with a total hospital stay of four days.

It is too early for definite conclusions about the efficacy of icatibant in ACE inhibitor-related angio-oedema, but two retrospective case series[6,7] show promising

results. Our experience provides a further observation. In life-threatening cases of this complication it is worth considering using this bradykinin inhibitor. Nevertheless, prospective studies are needed, including cost-effectiveness (30 mg icatibant (1 dose) costs €1750 (Shire Netherlands, March 2012)). Larger studies should be performed in a multicentre setting, but will be complicated.

REFERENCES

1. Agostoni A, Cicardi M, Cugno M, Zingale LC, Gioffre D, Nussberger J. Angioedema due to angiotensin-converting enzyme inhibitors. Immunopharmacology. 1999;44:21-5.
2. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet. 1998;351:1693-7.
3. Cugno M, Zanichelli A, Foieni F, Caccia S, Cicardi M. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. Trends Mol Med. 2009;15(2):69-78.
4. Landmesser U, Drexler H. Effect of angiotensin II type 1 receptor antagonism on endothelial function: role of bradykinin and nitric oxide. J Hypertens Suppl. 2006;24:S39-43.
5. Schmidt PW, Hirschl MM, Trautinger F. Treatment of angiotensin-converting enzyme inhibitor-related angioedema with the bradykinin B2 receptor antagonist icatibant. J Am Acad Dermatol. 2010;63:913-4.
6. Bas M, Greve J, Stelter K, et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. Ann Emerg Med. 2010;56:278-82.
7. Gallitelli M, Alzetta M. Icatibant: a novel approach to the treatment of angioedema related to the use of angiotensin-converting enzyme inhibitors. Am J Emerg Med. 2011. Nov 17. [Epub ahead of print]

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