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EDITORIAL

Generalism in journals of internal medicine

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As medicine is getting more and more complex and (bio) technology-driven, it is seeing a considerable increase in subspecialisation. This is not only true for traditionally 'broad' disciplines, such as internal medicine, surgery, or paediatrics, but in virtually all medical specialisms there is increasing sub-specialisation. We now see interventional cardiologists or cardio-electrophysiologists, fertility specialists, immuno-dermatologists, ophthalmologists who entirely focus on the anterior chamber of the eye, and ear-nose-throat specialists who only want to hear about the ear ossicles. It seems that the subspecialisation of all medical disciplines is evolving every year and is not going to stop for a while. Even more than in clinical practice, research is usually carried out in a small area of medicine and is subspecialised in itself. Hence, an increasing number of subspecialist journals are coming to press, whereas the number of general journals has been stable for decades. Nevertheless, most physicians, including subspecialists, still see patients with 'general' problems or problems belonging to a neighbouring subspecialism, or patients who also have problems other than those that fit in their subspecialisation. In view of that, it may be expected that the interest in medical journals that encompass more than subspecialised information and are not held by the boundaries of subspecialisation will remain. Indeed, journals such as the New England Journal of Medicine, the Lancet, the British Medical Journal and JAMA are widely distributed and read by a diverse readership on a weekly basis. National journals of medicine have a fixed position in the ranking list of medical journals in the Journal Citation Report and show an increasing impact factor.

This is also the case for the Netherlands Journal of Medicine, which shows an increasing position between the journal in the field of internal medicine and a rising impact factor.[1,2] The journal serves as a platform for clinicians and scientists to publish research and interesting clinical observations, not only from the Netherlands, but also from other countries (*table 1*). The fact that the majority of papers come from the Netherlands obviously reflects the nature of the paper but also the vitality of internal medicine in this country.[3] The increasing impact of the journal results in a yearly increase in submissions and with a fixed number of pages for publication this automatically means that the acceptance rate is dropping. This may be particularly true for some article categories, such as case reports and original papers (*table 1*). Nevertheless, the journal is able to publish more review manuscripts and interesting clinical observations can often be presented as a photo quiz (*figure 1*). The visibility of the journal is not only reflected by an increasing number

Table 1. *Number of submissions to the Netherlands Journal of Medicine in 2009 and in 2011 and acceptance rate (= published papers divided by submitted papers)*

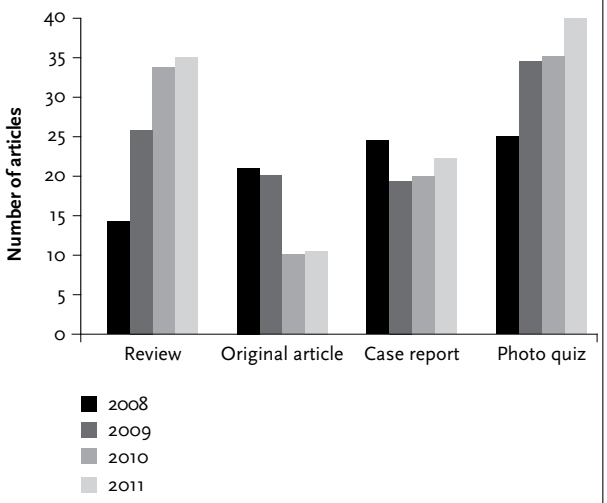
	Submitted		Acceptance rate	
	2009	2011	2009	2011
Total	328	444	30%	25%
Article type				
Review	35	45	74%	80%
Original article	107	71	19%	14%
Case report	136	244	14%	9%
Photo quiz	50	63	68%	63%
Special article	-	21	-	38%
Origin				
The Netherlands	61%	55%	39%	36%
Other European countries	16%	16%	23%	17%
North America	7%	6%	30%	29%
Rest of the world	16%	23%	4%	8%
Subdiscipline				
Cardiovascular	75	100	36%	33%
Respiratory	14	16	14%	25%
Gastroenterology	38	56	34%	28%
Intensive care	44	64	52%	43%
Haematology/Oncology	56	70	20%	29%
Rheumatology/ Immunology	21	24	29%	28%
Nephrology	23	35	22%	14%
Endocrinology	33	49	24%	17%
Infectious diseases	21	28	24%	27%
Other	3	2	0%	0%

Table 2. *Number of hits of various types of manuscripts in 2009 and 2010*

	Editorials		Reviews		Originals		Case reports		Photo quiz	
	n=11	n=11	n=17	n=34	n=20	n=10	n=27	n=20	n=22	n=35
	2009	2010	2009	2010	2009	2010	2009	2010	2009	2010
Mean number of hits/year	529	765	789	1432	402	876	445	654	415	1327
Maximum	941	1543	1034	2231	604	1432	578	1121	785	1977
Minimum	179	221	134	165	175	281	144	314	235	324

Mean number of hits per year for each section of the Netherlands Journal of Medicine, with maximum and minimum per category.

Figure 1. *Article types published in the Netherlands Journal of Medicine from 2008 until 2011*



of citations, but also by increasing downloads from our website. Some papers attract thousands of downloads and we have been able to show previously that this is closely related to citation of the article in other research papers.[4] *Table 2* shows the number of downloads of various types of manuscripts in 2009 compared with 2010. The top-3 most-downloaded papers in 2009 and 2010 are given in the reference list of this editorial (2009: references 5-7 and 2010: references 8-10, respectively).[5-10] Hence, in a rapidly subspecialising world of medicine and science, there is still ample room for a general clinical journal, both at the national and at the international level. The editorial team of the Netherlands Journal of Medicine hopes that 2012 will be another successful year for the journal and we are looking forward to publishing interesting and thought-provoking clinical research articles.

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REVIEW

New therapeutic options for immune thrombocytopenia

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ABSTRACT

Understanding of the mechanisms and aetiology of immune thrombocytopenia (ITP) has progressed significantly in recent years. It is now recognised to be an autoimmune condition, involving not only platelet destruction, but also deficits in platelet production. This has led to widespread research exploring potential mechanisms for therapy, the result of which has been the development of romiplostim and eltrombopag. These new treatments target the thrombopoietin receptor (TPO-R), promoting formation of megakaryocytes and survival of platelets.

Furthermore, the advances in the understanding of ITP have led to the production of guidelines to assist healthcare professionals in the diagnosis and treatment of ITP. This review examines the recommendations made in these guidelines, particularly the American Society of Haematology (ASH) 2011 evidence-based practice guidelines. In addition, searches were carried out to retrieve information on clinical trials of new molecules and off-label treatments for ITP.

Corticosteroids, anti-Rho(D) immunoglobulins (anti-D), intravenous immunoglobulins (IVIg) and splenectomy are well-established treatments and continue to be recommended in the guidelines. The recently available romiplostim and eltrombopag, which are specific for treatment of ITP, are also included in the recommendations. The only off-label therapy to be recommended in the guidelines is the chimeric monoclonal antibody rituximab. However, investigations are ongoing into products approved for other indications, which may be beneficial to patients suffering from refractory ITP.

KEYWORDS

Immune thrombocytopenic purpura, treatment, corticosteroids, intravenous immunoglobulin, splenectomy, rituximab, romiplostim, eltrombopag

INTRODUCTION

Since 1965 it has been recognised that platelet destruction caused by circulating antibodies is involved in the development of ITP.[1] In the 1980s it was suggested that ITP may also be attributable to megakaryocyte hypofunction. This was highlighted by the fact that platelet turnover was reduced in a high proportion of ITP patients.[2] Megakaryocytes are found in the bone marrow and are responsible for platelet production. When maturing, megakaryocytes express glycoprotein complexes GPIIb-IIIa and GPIb-IX on their surfaces.[3] In ITP, autoantibodies interact with these complexes, likely having a detrimental effect on the maturing megakaryocyte.[4]

In 1994, the American Society of Haematology (ASH) convened a panel to examine the treatment of idiopathic thrombocytopenic purpura. The outcome of this panel discussion was the practice guidelines, published in 1996.[5] Since then, the findings of a working group in 2008[6] and the ASH evidence-based practice guideline for immune thrombocytopenia (ITP) in 2011 were published. The term 'idiopathic' was removed as ITP is recognised to be an autoimmune disorder, with better understanding than this term would imply. 'Purpura' was removed[6] as bleeding and bleeding symptoms, are not present in all cases.[9]

The diagnosis of ITP continues to be one of exclusion. A diagnosis of ITP is reached in patients with a low platelet count and following elimination of possible secondary causes, for example: exposure to substances, including drugs, vaccines, herbs and foods; lymphoproliferative disorders; infection (including hepatitis C, HIV, cytomegalovirus); bone marrow transplant; and systemic lupus erythematosus (SLE).[8,10] The 2008 working group proposed that the platelet count threshold for the diagnosis of ITP should be <100x109/l as opposed to the commonly used threshold of <150x10^9/l. The rationale for this was the potential ethnic variations in platelet counts. Non-Western

ethnicities have been shown to have lower platelet counts,[11] and counts between 100 and 150x10^9/l are not uncommon and are asymptomatic.[8] In the 2011 guideline the 100x10^9/l threshold is adhered to. Treatment is only recommended for patients with counts <30x10^9/l.[6] Dutch treatment guidelines were published in 2010[7] and can also be found on the website of the Dutch Society of Hematology (www.hematologienederland.nl).

In Europe, the annual ITP incidence is around 3 per 100,000 people.[10] ITP tends to have a higher incidence in middle-aged females and male children.[13] Approximately half of all cases of ITP occur in children;[14] however, the focus of this review is the treatment options for ITP in adults.

METHODOLOGY

For this review the ASH Guidelines, consensus and working group reports[6,8,15,16] were examined along with their reference lists.

A search on PubMed was performed using the terms 'thrombocytopenic', 'purpura', 'therapy', 'treatment', 'therapeutics', 'humans' and 'adult', searching clinical trials, meta-analyses, practice guidelines, randomised controlled trials and reviews. The search was limited to articles in English, published between 1 January 2010 and 1 May 2011.

A search on ClinicalTrials.gov was performed with the search term of 'ITP' among phase II, III and IV trials in adults, thus identifying additional compounds currently in development.

MANAGEMENT OF ADULT ITP

Overview of established treatment

In general, patients with a platelet count below 20,000 to 30,000 10^9/l should receive treatment. Treatment is rarely started with a higher platelet count.[7,8] The primary first-line treatment is corticosteroids.[7,8] These are recommended for longer courses,[7,8] due to shorter courses being associated with a faster loss of response.[17] Other first-line treatments include anti-Rho(D) immunoglobulins (anti-D) or, if corticosteroids and anti-D are contraindicated or a rapid platelet increase is required, intravenous immunoglobulins (IVIg).[7,8] Splenectomy was recommended as second-line treatment for ITP in the 1996 guidelines[5] and remains so in the 2011 guidelines.[8]

New treatments

Two new compounds have recently been approved for use in the treatment of chronic ITP (second-line treatment) and represent a new class of therapeutic agents. These are the thrombopoietin receptor (TPO-R, also known as c-Mpl) agonists and thrombopoietic agents.

Thrombopoietin (TPO) is an endogenous growth factor, which directly activates the TPO-R of pluripotent stem cells, thereby stimulating formation of megakaryocyte colony forming units (meg-CFUs).[12,18,19] Activation of the TPO-R induces tyrosine phosphorylation of the Janus tyrosine kinases, Tyk2 and JAK2, and also the signal transducer and activator of transcription 3 (STAT3).[20] This leads to cell proliferation. It has been shown that patients who possess a mutation rendering them unable to produce TPO develop amegakaryocytosis leading to severe thrombocytopenia.[21] The TPO-R is also present on mature megakaryocytes and platelets, suggesting that TPO may also have a direct role in the survival of platelets.

Initial trials with cloned human TPO and similar molecules were unsuccessful.[22] In healthy human volunteers, these molecules were found to be immunogenic, causing the production of antibodies against them. These antibodies in turn acted against the subjects' own endogenous TPO causing thrombocytopenia.[22]

Further trials have focussed on compounds which bear no structural resemblance to endogenous TPO. Therefore, the likelihood of patients producing anti-TPO antibodies is reduced.[23] Romiplostim (a weekly 1 to 10 μg/kg subcutaneous dose) and eltrombopag (a daily 50 to 75 mg oral dose) are the first thrombopoietic agents approved for use in ITP.

Romiplostim

The recombinant Fc-peptide protein romiplostim (EMA approved February 2009) consists of two sections. These include one Fc (antibody) domain which lengthens romiplostim's half-life, and one peptide domain which is the section that binds to TPO-R. Romiplostim binds to the TPO-R as endogenous TPO does and activates the same Tyk2, JAK2 and STAT5 pathways resulting in megakaryopoiesis.[23,24]

In phase III clinical trials in both splenectomised and non-splenectomised patients, romiplostim was found to be well tolerated and effective. The target platelet count (50 to 200x10^9/l) was achieved within 3 weeks by over half of the patients. Of 125 patients studied, 83 received romiplostim and 42 received placebo. In the treatment arm, a durable platelet response (platelet count ≥50x10^9/l during ≥6 of the last 8 weeks of treatment) was achieved in 38% of splenectomised patients and 61% of non-splenectomised patients. In the placebo arms, 0% of splenectomised and 5% of non-splenectomised patients achieved a durable response.[12,25]

An additional open-label extension study was conducted for patients who had previously completed a romiplostim trial. As part of an interim analysis, data from 142 patients were

examined. Of these patients on romiplostim, 30% achieved a platelet response after the first dose and 57% after the third. Over the course of the study a platelet response was achieved in 87% of patients. No response was seen in 13% patients.[26]

The most common adverse event in patients receiving romiplostim in the phase III and extension studies was headache (35% and 37% of patients respectively).[25,26] Fatigue (33%, 30%), epistaxis (32%, 30%), arthralgia (26%, 25%) and contusion (25%, 30%) were the next most frequent.[25,26] The summary of product characteristics (SPC) also states that bone marrow reticulin formation occurred in four of the total 271 patients receiving romiplostim in studies.[27] In one patient who developed bone marrow reticulin formation, a follow-up bone marrow biopsy was carried out 14 weeks after discontinuation which showed improvement in the reticulin deposition.[19]

Eltrombopag

Eltrombopag (EMA approved March 2010) bears significant differences to romiplostim. It is a small, nonpeptide, organic molecule and is described as a TPO nonpeptide mimetic.[23]

Eltrombopag has an additive effect to TPO for which two possible explanations have been suggested. Eltrombopag either directly activates the signalling pathway without involvement of the TPO-R complex, or it binds with the TPO-R at a distance from the TPO binding location. The latter is considered the more likely, with histidine 499 and threonine 496 (in the transmembrane region of the TPO-R) believed to be either the targets or the mediators for binding.[18] The outcome of binding ultimately activates the same signalling pathways as endogenous TPO.[23]

Phase I studies showed that a single dose of eltrombopag was inefficacious. However, after eight days of daily treatment, a dose-dependant increase in platelet count was observed.[28]

A phase III clinical trial was conducted with 118 ITP patients. Splenectomised and non-splenectomised patients were eligible, as were treatment-naive patients and patients receiving concomitant ITP treatment. By day 43, a platelet response ($\geq 50 \times 10^9$/l) had been achieved in 81%, 70%, 28% and 11% of patients receiving 75 mg, 50 mg, 30 mg and placebo respectively. Platelet levels in the patients in the 50 and 75 mg groups increased to $>200 \times 10^9$/l in 37% and 50% of patients, respectively. Eltrombopag was therefore concluded to be an effective short-term treatment.[29]

Another phase III study in 197 patients showed that the median platelet count of patients receiving eltrombopag increased in the first week of treatment from 16 to 36×10^9/l. From day 15 until the end of treatment (6 months) the median platelet count remained between 53 and 73×10^9/l.[29] For patients receiving placebo, platelet counts never increased above 30×10^9/l.[31]

Similar to romiplostim, the most common adverse event with eltrombopag was headache. This was true in both the treatment and placebo groups (21%, 21%, 13% and 10% of patients in the placebo, 75 mg, 50 mg and 30 mg groups, respectively).[28] Headache is listed as the only very common undesirable effect in the eltrombopag SPC.[32] Transient increases in alanine aminotransferase (ALT, 9 patients) and bilirubin (5 patients) concentration were noted in phase III studies.[30] These transient increases were reported to have resolved either during treatment or following discontinuation.[30] However, it is advised that ALT and bilirubin levels are measured before and during treatment with eltrombopag.[32]

ITP REGISTRATION IN THE NETHERLANDS

With the introduction of these new drugs, there are better prospects for the patient with ITP. On the other hand, splenectomy remains an important treatment modality. Insight on long-term data on safety, quality of life and costs is important. With the registration of all patients with chronic ITP, the effects of treatment can be analysed. The ITP working group of the Dutch Society for Hematology developed an ITP registry. The quality of life is measured in collaboration with the Dutch ITP patient's society. Registration started mid 2011 and will continue for five years. Treating physicians are asked to collaborate to include patients into the registry (see www.hematologienederland.nl).

OFF-LABEL TREATMENTS

A number of medications are prescribed off-label to treat ITP with varying degrees of evidence and efficacy. For example, azithioprine, cyclophosphamide, cyclosporine, danazol, dapsone, etoposide, mycophenolate mofetil, procarbazine, rituximab and vincristine have all been investigated as possible ITP therapies. In this review, off-label therapies recommended in the 2011 ASH guidelines[8] and treatments appearing in the PubMed search are summarised.

Rituximab

Rituximab is a chimeric monoclonal antibody currently indicated for CD20 positive diffuse large B cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis.[33] Rituximab acts against the CD20 antigen which is found on the surface of B cells.[34] Following administration of rituximab, patients develop depletion of B cells.[35] The depletion of B cells leads to the patient's immune system being unable to produce the anti-GPIIb-IIIa and GPIb-IX antibodies.[34]

The first prospective, randomised, phase III clinical study of rituximab in ITP compared dexamethasone plus rituximab with dexamethasone alone in 101 treatment-naive patients. An improved sustained response (SR) rate (platelet levels of ≥50x10^9/l, six months after initial treatment) was seen in the patients in the dexamethasone plus rituximab group compared with dexamethasone (63% vs 36%).[34]

Another study in 62 patients receiving either glucocorticoids plus rituximab or glucocorticoids alone, showed no significant difference in overall response (80.6% and 74.2% respectively), complete response (67.7% and 54.8% respectively) or partial response (12.9% and 19.4% respectively). However, the same study showed that, of the patients who achieved response, SR was achieved in more patients receiving glucocorticoids plus rituximab than glucocorticoids alone (77.4% and 38.7% respectively).[36]

As rituximab is not currently licensed for use in ITP, safety information from the product label would not be pertinent for ITP patients. However, it should be considered that rituximab has immunosuppressant properties and therefore patients may have increased susceptibility to infections. Despite this, rituximab was generally well tolerated in the trials.[34,35] Rituximab is the only off-label therapy recommended in the 2011 ASH guidelines to be considered a second-line therapy.[8]

Mycophenolate mofetil (MMF)

MMF is available as a therapy to avoid rejection in transplant patients. It is also used off-label in a wide range of autoimmune diseases including Crohn's disease, autoimmune myasthenia gravis, rheumatoid arthritis and SLE.[37] MMF acts by inhibition of the enzyme inosine monophosphate dehydrogenase which affects the growth and maturation of lymphocytes, particularly T and B cells.[38] Similar to rituximab, this results in reduction of antibodies against the patients' megakaryocytes and platelets.

Clinical studies have been conducted with MMF and show promising results. In a study of 16 patients, MMF was administered 250 mg twice daily (bid), increased to 500 mg bid after one week and 1 g after two further weeks. A complete response (platelets of >100x10^9/l) was seen in 55% of patients and a partial response (>50 x10^9/l) in 45%. MMF showed greater effect in patients with fewer previous treatments.[36] Another study was conducted with 18 'highly refractory' patients (i.e. had failed to respond to other treatment including splenectomy), all of whom received MMF. Of these patients, five showed a good response (>30x10^9/l) and two showed partial response (no change in platelet count, but less requirement for other treatment).[39] Similar to rituximab, as MMF is not indicated for ITP, the safety data are not fully pertinent to ITP patients. As with rituximab, MMF is an immunosuppressant and prescribers should be aware of the potential for infection.

Amifostine

Amifostine is a cytoprotective agent. It is currently used to prevent renal toxicity in chemotherapy patients and to prevent xerostomia in patients receiving radiotherapy. Amifostine is inactive until dephosphorylated to its metabolite (WR-1065), which is able to enter cells. WR-1065 exerts a cytoprotective effect by scavenging free radicals, preventing damage to cell membranes and DNA.[40] Furthermore, amifostine has a protective and supportive effect on haematopoiesis and can inhibit apoptosis of haematopoietic cells.[41]

In a clinical trial of amifostine in 24 patients with refractory ITP, all patients showed elevated and stabilised platelet counts. All patients' platelet counts were >100x10^9/l at the end of treatment (400 mg, 5 times weekly for 4 to 5 weeks), except for two patients with platelet counts of >50x10^9/l.[41] Another trial in 17 patients demonstrated normal platelet counts in all patients after one course (four weeks) of treatment; all patients' platelet levels remained normal for two months following treatment discontinuation.[43]

Similar to other off-label therapies, amifostine's safety information is not specific to ITP patients. Only moderate adverse events were seen in the studies, including dizziness, nausea, vomiting, fatigue, and mild hypocalcaemia.[41] Of interest was that in patients whose platelet count had been normalised by amifostine and were administered concomitantly with atorvastatin or influenza vaccine, drops in platelet counts were observed.[42]

TREATMENTS UNDER CLINICAL EVALUATION

AKR-501

AKR-501 is a third thrombopoietic agent which is currently in clinical development. Similar to eltrombopag, AKR-501 is a TPO nonpeptide mimetic and acts in a non-competitive manner. AKR-501 has been shown to activate reporter molecules in TPO signalling pathways resulting in growth of megakaryocytes and TPO dependant cells.[19]

A phase II clinical trial using AKR-501 in approximately 65 patients was recently completed (March 2011), the results of which are not yet available.

AS1670542

AS1670542 is another second-generation thrombopoietic, small-molecule TPO agonist. AS1670542 mimics the action of TPO and has shown promising *in vivo* and *in vitro* results.[44]

Fostamatinib disodium

Currently in phase III clinical development for rheumatoid arthritis and phase II for ITP, fostamatinib disodium is a spleen tyrosine kinase (Syk) inhibitor. It is hypothesised that inhibition of Syk would lead to an amelioration of platelet destruction.[45]

Available phase II trial results show that of the 16 refractory ITP patients enrolled 75% responded to fostamatinib disodium. A sustained response was seen in 50% of patients. Gastrointestinal toxicity (diarrhoea in 6 patients and nausea in 4 patients) was observed, and was attributed to poor specificity of the agent.[45] Further studies are planned to evaluate the safety and efficacy of fostamatinib disodium in ITP patients.

CONCLUSION

Two drugs specific for ITP have recently become available and several established off-label pharmaceutical compounds are being researched for the treatment of ITP. Added to this, a number of molecules are currently in development, specific for the treatment of ITP. This combination of new approved therapies and vibrant research suggests that future prospects of therapy are promising for patients who suffer from ITP.

Physicians are asked to participate in registration of their patients with chronic ITP.

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REVIEW

New and existing pharmacotherapeutic options for persistent asthma and COPD

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ABSTRACT

Asthma and COPD are chronic inflammatory airway disorders with systemic manifestations. The two diseases have different airway inflammation, features of airway remodelling with subsequent pathophysiology and clinical presentation. The international management guidelines recommend stepwise pharmacotherapy depending on disease control and/or disease stage, comprising *relievers* and overall uniform *controller treatment*, despite the heterogeneity across the conditions and treatment response. Despite effective medications *per se*, still too many patients remain uncontrolled and no treatment can definitely cure either of the conditions. This overview includes currently recommended pharmacotherapeutic options with novel and future treatment targets.

KEYWORDS

Asthma, COPD, pharmacotherapy, anticholinergics, beta2 agonists, xanthines, inhaled corticosteroids, leukotriene modulators, PDE-inhibitors, anti-IgE, anti-cytokines

INTRODUCTION

According to GINA (Global Initiative for Asthma, 2010), there are currently over 300 million people suffering from asthma worldwide; the prevalence is still increasing especially among children.[1] Despite overall effective treatment options and uniform management guidelines, there is apparently still room for improvement. Based on a large cross-sectional study involving Asthma Control Test (ACT) scores in almost 8000 adults and over 3000 children from 29 countries worldwide, still too many asthmatics appeared sub-optimally controlled.[2] A similar conclusion can be drawn from the Gaining Optimal Asthma control (GOAL) study, where approximately 30% of almost 3500 patients failed to reach 'optimal' asthma control, despite sustained maximal therapy with the gold standard combination (inhaled corticosteroids and long-acting beta2-agonists)[3] and from more recent studies which reported up to 59% of asthmatics from primary care failing to reach control.[4,5]

Chronic obstructive pulmonary disease (COPD) is a major cause of premature death with approximately 600 million sufferers worldwide.[6,7] The prevalence is raising mainly due to an increasing number of smokers. Epidemiological surveys previously showed that 0.1 to 1.5% of individuals have severe obstructive lung disease, defined as FEV1 of <50% of predicted.[8] More recent data, notably the PLATINO[9] and the BOLD[10] surveys, highlighted the prevalence of COPD GOLD stage I and onwards of 7.8 to 19.7% in a population of certain Latin Americans and the prevalence of COPD GOLD stage II and onwards of a mean of 10.1% in smokers of a globally more representative population sample, respectively. Few epidemiological studies exist on the prevalence of COPD GOLD stage IV disease, and therefore it is often the opinion that figures on the number of COPD patients at all stages are significantly underestimated.[11-13]

In the past two decades, the development and validation of several non-invasive inflammometric methods and assays has greatly contributed to our understanding of the pathophysiological backgrounds, disease phenotyping and identification of potential targets for customised therapies.[14-17] In the updated GINA guidelines, this

paradigm became manifest as control-directed disease management in contrast to the previous approach based on symptoms and lung function parameters.[1] For COPD, it appears that the level of clinical, pathological and genetic heterogeneity that exists across patients has undermined potential advances in COPD pharmacotherapy. So far, there is no disease-modifying pharmacotherapy available and smoking cessation is the cornerstone of causal COPD management with additional, stage-dependent, mainly one-size-fits-all, symptomatic pharmacotherapy.[6] Given the multifaceted and heterogeneous aetiologies of asthma and COPD, optimal disease management should consist of customised treatment following accurate phenotyping. Such customised or phenotype-directed therapy should include targeted pharmacotherapy, combined with patient education, lifestyle adjustments, avoidance of noxious airway irritants, co-treatment of comorbidities and (if needed) additional therapies (revalidation, oxygen, etc.) along with adequate monitoring of the effects of disease management.[18]

In this review we aim to provide a link between disease subsets of chronic inflammatory (obstructive) airways disease to current treatment options according to international guidelines and to some novel, (targeted) pharmacotherapeutic modalities.

FROM PATHOGENESIS TO TARGETED TREATMENT

Background

Both asthma and COPD are chronic inflammatory airways diseases, although there are local and immunological differences (*figures 1A-C*). Apart from their local presentations, both conditions possess systemic components. Asthma is often associated with allergy. The airway inflammation in allergic asthma is predominantly T-helper 2 cell-driven with mast cells, eosinophils and basophils as the key effector cells (*figure 2*). In more severe asthma other inflammatory mechanisms (Th-1-cells, neutrophils) and structural cell defects (e.g. epithelial and airway smooth muscle cells) may prevail while comorbidities (e.g. obesity, smoking, etc.) often play an important role in its pathophysiology.[14,19-21] In some asthmatics, inflammatory markers, such as allergen-specific IgE, cysteinyl leukotrienes, IL-5 and TNF-alpha, were shown to play a prominent role in the pathophysiology of their asthma.[14] Targeting these

Figure 1A. *Bronchial biopsy from a steroid-naive asthmatic patient: Bronchial wall shows extensive eosinophil infiltration and thickening of the basement membrane*

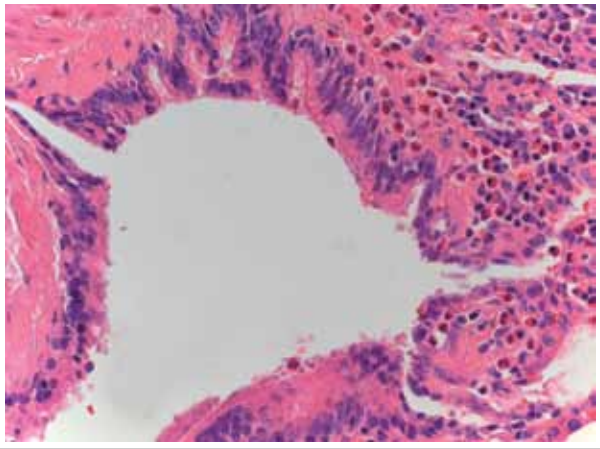


Figure 1B. *Bronchial biopsy from an asthmatic patient showing eosinophilic infiltration and hyperplastic bronchiolar smooth muscle*

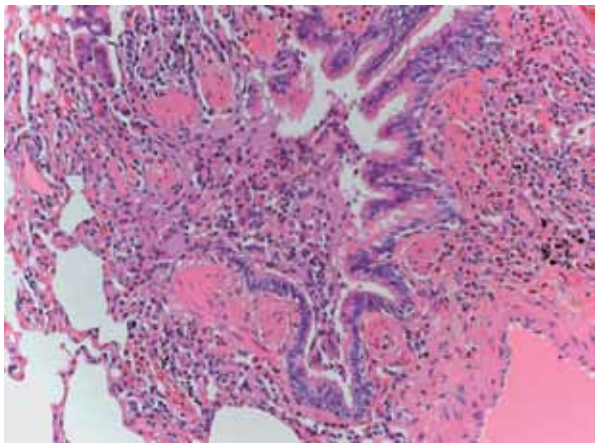


Figure 1C. *Bronchial biopsy taken from a patient with chronic bronchitis, showing epithelium with goblet cell metaplasia and increased number of inflammatory cells, particularly lymphocytes (left corner) and hyperplastic smooth muscle*

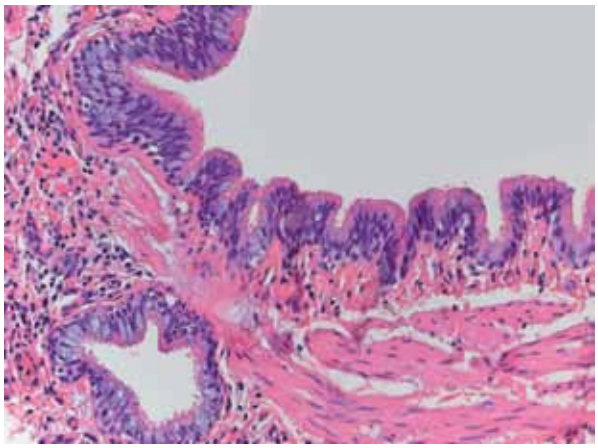
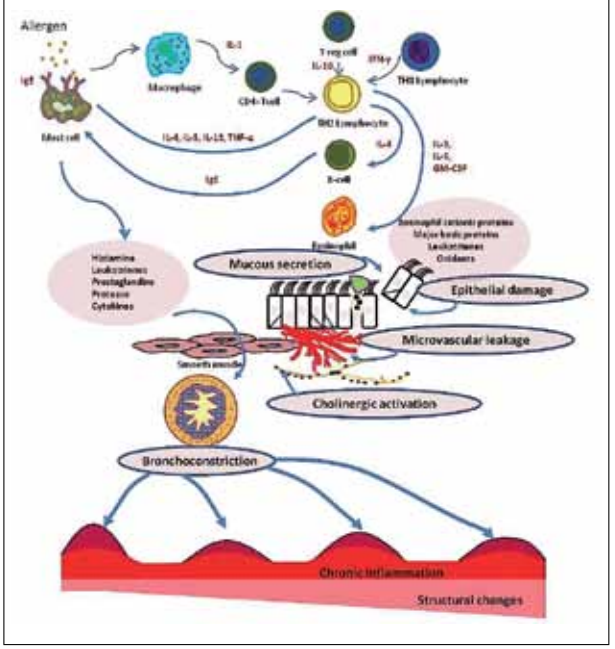


Figure 2. *Th-2 cell driven airway inflammation in allergic asthma*



inflammatory markers may offer attractive treatment options in some asthma phenotypes.[22] Within the asthmatic airways, inflammatory events along with structural changes ('airway remodelling') have been shown to induce airway hyperresponsiveness to (non) specific stimuli, and if untreated, to produce variable symptoms, exacerbations and pathophysiological signs.[1] Within an asthmatic individual, the degree of bronchoconstriction (generally measured by FEV1 and expressed as % of predicted value or by FEV1/FVC ratio) may vary over time. Depending on asthma control, lung function can be within normal ranges or reduced to some degree, although mostly fully reversible.[1] During the last decade, small airway involvement in uncontrolled asthma and COPD has drawn increasing attention.[23,24] Clinical outcomes that have been found to correlate with uncontrolled small airway inflammation include exacerbations, exercise-induced bronchoconstriction and nocturnal asthma. Targeting the small airways has become part of treatment strategies through the development of small particle formulations inhaled by innovative devices and systemically active compounds along with the introduction of several tools for monitoring of the small airways function and inflammation.[23]

Emphysema and chronic bronchitis are two major subsets of COPD. Tobacco smoking is a major aetiological factor in the pathogenesis of COPD, which clinically presents with progressive dyspnoea, (productive) cough and a fixed, progressive bronchoconstriction and hyperinflation with declining lung function.[6] Clinically, it may be difficult to discriminate some asthma subsets – especially smoking asthmatics – from full-blown COPD.

Within the chronic airway inflammation of COPD, macrophages, CD8+ T lymphocytes and neutrophils are the key effector cells, releasing toxic mediators contributing to airway destruction and remodelling.[25,26] Destruction of alveolar tissue in emphysema is thought to be caused by the release of proteinases (e.g. matrix metalloproteinase from alveolar macrophages) or as a consequence of an autoimmune response (e.g. CD8+ T lymphocytes).[27,28] Goblet cell hyperplasia and enlargement of submucosal glands contribute to the excessive mucus production especially seen in chronic bronchitis. Peribronchiolar fibrosis within distal airways can induce disruption of the parenchymal attachments to small airways promoting collapse on expiration and hyperinflation.[29]

Asthma severity and phenotypes

Steroid-naive asthma can be classified according to its severity based on variability in symptoms and bronchoconstriction, ranging from intermittent to (mild, moderate and severe) persistent.[1] In general, milder forms are associated with allergy, characterised by a T-helper 2 cell-driven profile with often high levels of specific IgE, airway eosinophilia and increased release of cysteinyl leukotrienes (*figure 2*).[30] In up to 80%, allergic asthma is associated with allergic rhinitis and often becomes manifest at a younger age.[31] This phenotype generally responds well to standard therapy consisting of allergen avoidance and inhaled corticosteroids and/or leukotriene modulators and anti-IgE.[1,31] In contrast, the severe persistent or 'refractory' phenotype is a more heterogeneous disorder, which can be subdivided into several clinical subsets with different (e.g. Th-1 driven, neutrophilic) or more pronounced airway inflammation (small airways) and/or structural cell defects (e.g. epithelial and airway smooth muscle cells), often associated with comorbidities (*table 1*).[14,19-21,23,32]

In view of the heterogeneity in clinical presentation, immunopathology and response to treatment, it may sometimes be helpful to include as many asthma determinants as possible for an adequate evaluation.[15-17,33,34] To aid diagnosis and effective treatment, several classifications for asthma phenotyping have been suggested. Although none are fully standardised, a feasible subtyping has been proposed by Sally Wenzel based on clinical or physiological phenotypes, phenotypes related to triggers and phenotypes related to the predominant inflammatory airway response (*table 1*).[14] Inevitably, there is a substantial overlap across the phenotypes and novel detection techniques in preferably non-invasive airway samplings should help to link the underlying immunological substrates to the clinical and pathophysiological presentation to accurately define an individual's

Table 1. *Asthma phenotypes and targets, modified from references 14, 21,and 23*

Clinical or physiological phenotypes
Defined by age of onset
Defined by asthma severity
Defined by chronic restriction
Exacerbation prone/brittle asthma
Treatment-resistant/refractory asthma
Phenotypes defined by:
External triggers
Exercise and cold, dry air
Ozone
Environmental allergens, respiratory viruses and irritants
Occupational allergens or irritants
Oxidative stress-inducers: (passive) tobacco smoke, air pollution, airway infections
Aspirin or non-steroidal anti-inflammatory drugs
Interfering drugs (e.g. beta-blocking agents, ACE inhibitors)
Endogeneous factors and comorbidities
Chronic rhinosinusitis
Hormonal (e.g. menses)
Obesity
Gastro-oesophageal reflux disease
Psychosocial and emotional factors (disease understanding and awareness, stress, compliance)
Inflammatory phenotypes
Cellular
Eosinophilic
Neutrophilic
Mixed cellularity
Pauci-granulocytic
Predominant mediators
Cysteinyl leukotrienes
Prostaglandins
IgE
IL-5
TNF-alpha
Important structural determinants
Epithelial cells
Dendritic cells
Glandular cells
Airway smooth muscle cells
Small airways

phenotype and customised (targeted) therapy.[33,35] Recently, a large international project entitled 'Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes' (U-BIOPRED), initiated by Sterk and colleagues, has started and its aim was to identify, analyse and validate biomarkers for phenotyping and customised treatment of severe refractory asthma.[35]

COPD severity stages and clinical phenotypes

In analogy with GINA, COPD is staged according to the severity of symptoms and (postbronchodilator) lung function impairment in GOLD stages I-IV.[6] Tobacco smoking is the major inducer and therefore smoking cessation is the cornerstone in the management of all COPD stages. Similarly to asthma, COPD also represents a heterogeneous group of airway disorders, with emphysema and chronic bronchitis as the commonly known clinical phenotypes (*table 2*).[6] A recent proposal by a workgroup suggests COPD phenotyping by disease determinants including clinical presentation, response to therapy, frequency of exacerbations, systemic presentation, pathophysiological parameters, radiological characterisation and inflammatory markers to enable identification of prognostic and therapeutic subgroups.[36] This approach awaits validation.

The key COPD characteristics include chronic inflammation of the proximal and distal airways, driven

Table 2. *Major determinants of COPD phenotypes*

Clinical, physiological phenotypes and comorbidities
Emphysema
Chronic bronchitis
Defined by COPD severity
Frequent exacerbator
Bullous emphysema
Concomitant asthma
Respiratory failure (hypercapnia/hypoxia)
Cardiac failure (right/left ventricle)
Phenotypes defined by:
External triggers
Cigarette smoking (history)
Occupational dust, vapours and fumes (e.g. indoor air pollutants, coal, straw, animal dung, crop residues and biomass fuel)
Oxidative stress-inducers: air pollution, airway infections
Endogeneous factors
Alpha1- antitrypsin deficiency
(Systemic) inflammatory phenotypes
Cellular
Neutrophilic
Macrophages
Epithelial cells/fibroblasts/fibrocytes
Soluble inflammatory markers
C-reactive protein
Serum amyloid A
Leukotriene B4
Proteases
Mucines (MUC5AC)
IL-1, IL-6, IL-8, TNF-alpha

by several inflammatory cells and mediators and associated with airway remodelling and tissue destruction.[15,37,38] Within a specified COPD phenotype, these features may clinically present as a combination of one or more of the following symptoms and signs: dyspnoea, mucus hypersecretion, chronic cough with sputum production, fixed airway obstruction, hyperinflation and (frequent) exacerbations. Emphysema is characterised by alveolar wall destruction causing irreversible enlargement of air spaces distal to the terminal bronchioles. Chronic bronchitis is clinically defined as daily cough with (excessive) production of sputum for at least three months, two years in a row.[6,39] Histopathologically, there is evidence of mucus gland hyperplasia with mucus hypersecretion leading to chronic cough and sputum production. In addition, chronic bronchitis also presents with inflammation and swelling of the epithelial lining and submucosa of the airways causing narrowing and obstruction of the lower airways and chronic bronchiolitis. These sequelae typically lead to the increased prevalence of bacterial lung infections manifesting as frequent exacerbations.[40] More recently, evidence was provided that the abnormalities seen in COPD are not only restricted to the airways, but often also systemically present.[41,42]

PHARMACOTHERAPEUTIC OPTIONS FOR ASTHMA AND COPD

Guidelines

Awareness and avoidance of relevant triggers (e.g. tobacco smoke, occupational and domestic irritants, specific allergens, medications and tobacco smoke) is often the first step in the management of both asthma and COPD. Based on the severity or level of disease control, most guidelines pragmatically recommend a one-size-fits-all, stepwise approach to pharmacotherapy, consisting of relievers (bronchodilators) and controllers (immunomodulator and/or anti-inflammatory agents) in combination with treatment of comorbidities.[1,6,31] Although efficacious in some asthma subsets, allergen-specific immunotherapy will not be discussed in this review given its specific scope and currently ongoing innovations.[43]

Current pharmacotherapy and applications

Anticholinergics

Since the late 1970s, anticholinergic drugs have been developed for the treatment of chronic obstructive airway diseases. Ipratropium (Atrovent®, Iprapropium®, Ipraxa®) and the long-acting tiotropium (Spiriva®), marketed in the beginning of the 2000s, antagonise the effect of acetylcholine at the M1 and M3 muscarinic receptors within the airways, resulting in bronchodilation and a reduction in mucus production. The bronchodilator effect usually starts within 15 minutes post-inhalation and lasts for approximately three to eight hours.

Despite a predominant role in the treatment of COPD, anticholinergics may also benefit asthmatics with congenital adverse responses to beta2 agonists—up to 20% of the asthma population.[44] In addition, during an acute exacerbation when response to SABAs may be poor, a combination with an anticholinergic agent generally provides faster relief.[45] In a recent three-way, double-blind, triple-dummy, cross-over study in 210 patients with inadequately controlled asthma, addition of tiotropium to low-dose ICS during 14 weeks of treatment showed comparable therapeutic efficacy to salmeterol and was superior to doubling of the ICS dose.[46] Similarly, in a double-blind, placebo-controlled, parallel study in B16-Arg/Arg patients with uncontrolled asthma, addition of tiotropium to a moderate dose of ICS was comparably effective to salmeterol in maintaining lung function.[47]

In COPD, a combination of a beta2 agonist with an anticholinergic is often applied as part of the maintenance treatment for optimal efficacy and to reduce the occurrence of any side effects (registered fixed combinations: fenoterol/ipratropium (Berodual®), salbutamol/ipratropium (Combivent®, Ipramol®, Ipratropium/salbutamol FNA).

Both ipratropium and tiotropium have a low systemic bioavailability and hence are associated with few systemic side effects. The most commonly reported side effects include dry mouth, acute urinary retention, gastrointestinal problems, arrhythmias and headache.[48,49] Anticholinergics should be used with caution in patients with prostatic problems and in those susceptible to angle-closure glaucoma. Importantly, during the four years of the UPLIFT study, no evidence of increased (death from) cardiovascular events, arrhythmias or stroke was observed in COPD (stages II-IV) patients treated with tiotropium.[50,51]

Presently, several long-acting LAMAs are being developed and are in different developmental phases, e.g. *Aclidinium*, LAS35201, GSK656398, GSK233705, NVA237 (glycopyrrolate), ORM3, CHF5407 and QAT370.

Beta2-adrenoceptor agonists

Soon after its launching in 1968, the short-acting beta2-receptor agonist (SABA) salbutamol became the most widely used fast-acting reliever medication for asthma and COPD.[1] The success of salbutamol initiated the development of several other short-acting beta2 agonists (SABAs), including carbuterol, clenbuterol and fenoterol, with a fast onset (within five minutes of inhalation) and with a duration of action up to six hours. A further step came in the 1980s with the development of long-acting beta2 agonists (LABAs). Salmeterol (a partial beta2-adrenoceptor agonist) with a slow onset and a duration of action up to 12 hours, was first launched followed by formoterol (a full beta2-adrenoceptor agonist)

combining a similar duration of action with an onset of action comparable to salbutamol. Indacaterol (Onbrez®), a partial beta2-adrenoceptor agonist with a similarly fast onset of action as salbutamol and a 24-hour duration of action, was launched in Europe and the USA in the past year and is currently only registered for the treatment of COPD.[52] In the patient studies so far performed, this ultra-LABA has not shown any tachyphylaxis. Presently, several ultra-long-acting LABAs (ultra-LABAs) e.g. carmoterol, vilanterol trifenatate, olodaterol, GSK-159797 and GSK-642444 with a sustained bronchodilation up to 24 hours are being developed, creating the possibility of once daily dosing.[53] The mechanism of action of beta2 agonists is predominantly bronchodilator through airway smooth muscle relaxation, with modest anti-inflammatory activity encountered in some studies.[54,55]

Current guidelines recommend SABAs as rescue therapy only on (as infrequent as possible) 'as needed' basis.[1] This is based on the insight that asthma is a chronic inflammatory condition and that targeting airway inflammation should be the primary goal in treatment of persistent asthma in contrast to symptom control as the primary focus. Moreover, several studies showed that maintenance therapy with SABAs and LABAs — even if combined with ICS — may potentially mask the airway inflammation.[56,57] In addition, maintenance therapy with LABAs (*plusminus* ICS) has been shown to induce tolerance to their bronchoprotective effects and cross-tolerance to the reliever effects of SABAs.[58-61] Although not a consistent finding,[62] some studies showed a decreased therapeutic response to beta2 agonists in patients with a homozygous variation for arginine (Arg/Arg) at codon 16 of the beta2-adrenergic receptor.[44,63] In patients with this polymorphism, regular treatment with the short-acting beta2 agonist albuterol was associated with a significant decrease in lung function over time.[63] Some of these deleterious effects during long-term use of LABAs with or without an adequate dose of ICS may have resulted in an increased morbidity and even reported asthma deaths.[64] Present guidelines, therefore, recommend maintenance therapy with LABAs only in combination with appropriate doses of corticosteroids in the more severe disease (asthma treatment steps 3-5).[1]

In COPD from GOLD stage II onwards where sustained bronchodilation is required, maintenance therapy with long-acting beta2 agonists is recommended, either alone or in combination with a LAMA.[6] The development of ultra-LABAs represents a promising advance in the treatment of COPD, enabling (future) combinations with a LAMA, and providing superior efficacy through improved patient convenience and compliance.

Xanthines

Several xanthines are known to positively affect the breathing function, including aminophylline and to a lesser extent caffeine and theobromine. From the late 1930s until the 1970s, theophylline, a weak and nonselective phosphodiesterase (PDE) inhibitor, became the most widely prescribed reliever for obstructive airway disease.[65,66] Although theophylline is known to offer a substantial bronchodilation within the (narrow) therapeutic range (approximately 10 to 20 μg/ml), serious side effects inevitably occur at higher plasma levels.[66] The most common adverse reactions include cardiovascular side effects (arrhythmias), gastrointestinal (nausea) and CNS symptoms (headache, seizures).[66,67] These disadvantages and the advent of the superior beta2 agonists and tiotropium resulted in theophylline's relegation to second/third line (asthma and COPD) treatment option in developed countries during the 1980s.[68-70] In recent years, interest in the xanthine derivatives has revived due to their oral formulation, low cost and the discovery of the PDE-receptor subtypes. Moreover, some evidence pointed to potential anti-inflammatory activity,[71,72] partly through the suppression of the inflammatory gene transcription by activation of histone deacetylase2 (HDAC2), which is the key target for corticosteroids.[73] This mechanism may explain the beneficial effects on asthma control reported by several investigators when combining (low-dose) theophylline with inhaled corticosteroids (ICS).[74,75] Recently, additional anti-inflammatory effects have been reported, including the acceleration in eosinophil apoptosis and the decrease in recruitment of lymphocytes and neutrophils into the airways.[71,76] These properties may be promising in the treatment of severe asthma and COPD. Although initially classified as a nonselective PDE inhibitor, the pharmacological effects of theophylline appear much broader and include, among others, antagonism of adenosine and phosphoinositide-3 kinase (PI3K).[77,78] Oral slow-release tablets (theolair) are the commonly available formulation of xanthines, usually prescribed in a twice daily maintenance dose. In parallel with the renewed interest in theophylline and the discovery of several PDE (receptor) subtypes, there has been development of more specific PDE inhibitors for the treatment of chronic inflammatory/obstructive airway disease in the last decade – see section below.[79] Targeting PDE-3 has been shown to produce bronchodilation.[80] Future studies in asthma applying combined PDE inhibitors (e.g. PDE3/4) should demonstrate their putative superior effectivity.[80]

Inhaled corticosteroids

In the early 1970s, the first topically active, aerosolised corticosteroid, beclomethasone dipropionate (BDP), was registered for treatment of inflammatory airways diseases.[81,82] This inhaled ICS showed efficacy in the treatment of asthma without the adverse effects associated with systemic corticosteroids. However, the widespread

use of ICS came some 20 years later, most likely as a result of the paradigm switch that asthma is an inflammatory disease and the subsequent effect on the concurrent guidelines for asthma treatment.[1]

Presently, inhaled corticosteroids are the first-choice controller agents for the treatment of persistent asthma.[1] The beneficial effects are mediated through interaction with intracellular corticosteroid receptors present within several cells, resulting in suppression of inflammatory gene transcription and activation of anti-inflammatory gene transcription.[83,84] Prolonged treatment with ICS produces sustained anti-inflammatory efficacy with subsequent improvement in asthma control both in adults and children.[85,86] However, ICS are less effective in patients with severe asthma and in COPD, partly due to the different inflammation (neutrophilia) and extensive structural changes within the airways, inability to (sufficiently) reach all parts of the airways, comorbidities or exogenous factors.[23,87] Particularly, tobacco smoke is known to induce oxidative stress with subsequent airway neutrophilia and the down-regulation of histone deacetylase (HDAC2) activity, thus contributing to corticosteroid resistance.[88]

In COPD, guidelines recommend ICS as maintenance therapy from GOLD stage III (with frequent exacerbations) and onwards in spite of their questionable long-term efficacy.[6] The dry powder and pressurised metered-dose inhalers contain either a mono-compound (beclomethasone, fluticasone, mometasone, ciclesonide or triamcinolone) or a combination with a LABA. The (fixed) combination of a corticosteroid with a LABA has prompted a number of studies which showed notable improvements in FEV1[89-92] and HRQoGRL, including a reduced decline in FEV1 and exacerbations in COPD patients (GOLD stages II-III) over time.[93-95] Although most studies have been unable to demonstrate a significant or clinically meaningful reduction in the FEV1 decline in the long term, two recent large studies, TORCH[96,97] and GLUCOLD[98], examining the long-term clinical efficacy of the fixed combination ICS and LABA in COPD (stages II-III), came close to challenging this premise. In contrast to placebo and both monotherapies, the TORCH data suggest a synergy between fluticasone (FP) and salmeterol reflected in superior efficacy on several disease-related parameters including the FEV1 decline; however, the primary parameter, i.e. reduction in mortality after long-term use of the combination, failed to reach statistical significance.[96,97] In addition, the GLUCOLD study clearly showed that corticosteroids with or without LABA effectively reduced inflammatory cells in sputum and bronchial biopsies while slowing down the decrease in FEV1 in some COPD subsets.[98] A subanalysis[99] showed that different inflammatory phenotypes within COPD may respond differently to (gold standard) pharmacotherapy. These findings warrant characterisation of inflammatory phenotypes within COPD to enable customised (targeted) treatment modalities.

In the past two decades, modification of the initial compounds and inhalers increased their potency and first-pass metabolism in combination with an improved lung deposition. Presently, available ICS differ little in clinical efficacy and side effects: fluticasone and budesonide being the most widely used alone or in combination with a LABA in one inhaler device. The most recently launched innovative ICS is ciclesonide, which is delivered as an inactive prodrug.[100] The pharmacological properties of ciclesonide in combination with the inhaler properties (solution-based HFA MDI) and small particle size result in an optimal lung deposition and distribution including the small airways with an overall low systemic bioavailability.[101] Based on its pharmacokinetic and pharmacodynamic properties, ciclesonide combines the advantages of a prolonged activity (once daily use) with less (local and systemic) side effects which may positively affect patient compliance.[100,102,103] Like most of its competitors, ciclesonide produces comparable improvement on asthma control and QoL across all disease severities.[103]

ICS-related side effects can manifest both locally and systemically. The most commonly reported local side effects comprise of oral candidiasis, hoarseness and dysphonia,[104] while systemic side effects, such as easy bruising, cataract and osteopenia, are usually restricted to chronic use of high ICS doses.[87,105]

Although ICS cannot cure chronic inflammatory airway diseases, they are the mainstay of anti-inflammatory therapy for these conditions. Addition of a LABA may potentiate anti-inflammatory activity of ICS.[106,107] The currently available fixed ICS/LABA-combinations include: fluticasone propionate/ salmeterol (Seretide®/Advair®/ Adoair®) budesonide/formoterol (Symbicort®) and beclometasone/formoterol (Foster®).

Future compounds in this drug class presently under development now focus on a favourable therapeutic index including small airway deposition and once daily dosing. The novel once-daily combination of fluticasone furoate/ vilanterol trifenatate (Revolair™), now in phase III, is aimed to eventually supplant Seretide.

Targeted pharmacotherapies

Leukotriene modulators

Leukotrienes (LTB4, LTC4, LTD4, LTE4) are pro-inflammatory mediators, synthesised from arachidonic acid via the 5-lipoxygenase (5-LO) metabolic pathway. Especially the cysteinyl leukotrienes (CysLTs: LTC4, LTD4, LTE4), synthesised by activated mast cells and eosinophils, have been shown to play an important role in the pathophysiology of several asthma phenotypes, including 'asthma rhinitis' and aspirin-exacerbated airway

disease (AERD).[108,109] CysLTs possess pro-inflammatory, broncho and vasoactive properties and have been shown to induce several features of asthma, including airway inflammation and airway hyperresponsiveness, both in healthy subjects and in asthmatics. These observations have driven the development of several anti-leukotriene agents in the 1980s-1990s as the first systemically active, targeted therapy for asthma.[110] Two main categories of leukotriene modulators have been developed and mainly evaluated in asthmatics: leukotriene synthesis inhibitors (LTSI), i.e. 5-LO-inhibitors and 5-LO activating protein (FLAP) inhibitors that block the synthesis of all leukotrienes at the 5-LO level and leukotriene receptor antagonists (LTRA) that inhibit the effects of CysLTs at the CysLT1 receptor.[108] As opposed to the gold standard (ICS) controller therapy, leukotriene modulators possess targeted activity that acts throughout the entire bronchial tree, which is from the upper airways down to the small airways, thereby combining anti-inflammatory (mainly anti-eosinophilic) properties with (modest) bronchodilator and bronchoprotective effects against nonspecific and specific stimuli.[111,112] So far, zileuton (Zyflo™) is the only LTSI licensed for the treatment of asthma in USA only. Due to its modest potency and potential liver toxicity, this four times daily oral drug has now been largely superseded by the more potent, LTRAs (zafirlukast (Accolate®) and montelukast (Singulair®), respectively) with more favourable safety and pharmacokinetic profiles.

To date, montelukast is the most widely used leukotriene modulator for the treatment of asthma and has been prescribed to over 25 millions of patients including approx. 6.5 millions of young children. Both as monotherapy and in combination with inhaled corticosteroids, montelukast showed clinical efficacy in asthmatic patients, improving symptoms, lung function, exacerbation rates and quality of life in both adults and children.[109,113] Several studies provided evidence that addition of an LTRA can improve several aspects of asthma especially in CysLT-driven asthma-phenotypes, such as with asthmatic patients with concomitant allergic rhinitis.[114-116]

The most commonly described side effects are generally mild and comprise headache, flu and gastrointestinal complaints. Neuropsychiatric events, including anxiety, depression and suicidality, were reported in rare cases but appeared unrelated to montelukast.[109] In addition, Churg-Strauss syndrome (CSS) has been mentioned in relationship to treatment with montelukast; however, the incidence is similarly low to that in the general population and often associated with tapering off of oral corticosteroids in the more severe asthma.[109]

GINA guidelines recommend low-dose ICS or a leukotriene modifier as controller therapy in step 2 of the asthma management in adults and children older than 5 years.[1] In the subsequent treatment steps 3 and 4, a leukotriene modifier is included as add-on therapy to ICS.[1] Similar recommendations are made by paediatric GINA guidelines, advocating a leukotriene modifier as an alternative to low-dose ICS for the first controller step and as add-on therapy for the subsequent treatment steps in children aged 5 years and younger.[117] According to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, LTRA should also be considered in patients with allergic rhinitis with or without concomitant asthma.[31]

So far, no leukotriene modulators have been implicated in the treatment guidelines of COPD.[6] In COPD, LTB4 plays a more prominent role than CysLTs, and hence, LTSI may be more effective in COPD than LTRA.[118,119] Presently, there is an interest in leukotriene modifiers and there are several compounds under development, e.g. the FLAP inhibitor GSK2190915 (AM103) and the 5-LO-inhibitors Setileuton and MK-0633 aimed for treatment of conditions including (severe) asthma and COPD.[120-122]

Selective PDE inhibitors

Phosphodiesterases form a superfamily of at least 11 isoenzymes (PDE1-11), which are involved in several biological and inflammatory processes within the human body. Each iso-enzyme has a unique tissue subdivision and different properties allowing targeted therapy with potentially fewer systemic side effects especially when compared with nonselective PDE inhibition.[123] In the past two decades, there is increasing interest in the development of selective PDE inhibitors for potential treatment in asthma and/or COPD.[124] Especially the PDE4 isoenzyme seems a promising target for anti-inflammatory and disease-modifying therapy as it regulates the function of several immune, inflammatory (neutrophils, macrophages) and structural cells (e.g. airway smooth muscle) involved in the pathophysiology of chronic inflammatory and obstructive airways disease.[123] So far, the majority of the clinical COPD studies have been performed with the second-generation oral PDE4 inhibitors cilomilast and roflumilast, of which roflumilast combines a superior pharmacological profile (once daily dosing) with a favourable therapeutic index.[124] In several preclinical studies, selective roflumilast reduced neutrophilic inflammation and features of airway remodelling (see Rabe and the references therein).[125]

Although the result of the early phase III findings showed consistent but small improvements in lung function, the effects on exacerbations remained inconclusive.[126] A post-hoc analysis of these studies revealed a defined subset of COPD patients likely to benefit from roflumilast, with severe COPD associated with chronic bronchitis.[127] This hypothesis was subsequently tested in two randomised, controlled one-year phase III studies of identical design.[128] In these studies, in patients with chronic bronchitis, severe airway flow limitation and a history of frequent

exacerbations, treatment with roflumilast significantly reduced moderate to severe exacerbations and was again superior to placebo on lung function parameters. This efficacy was independent of concomitant treatment with LABA.[128]

In two supplementary six-month studies in patients with COPD with moderate to severe airway flow limitation, roflumilast (500 μg once daily) provided incremental improvements in pre- and post-bronchodilator FEV1 when given on top of salmeterol or tiotropium, respectively.[129] The most commonly reported roflumilast-related side effects include headache, insomnia, nausea, diarrhoea and weight loss (mean 2.1 kg). The majority were mild to moderate in intensity, appeared early but resolved over time.[128,129]

So far, no studies have compared the efficacy of roflumilast versus ICS. However, a recently published post-hoc analysis of the sub-group of patients concomitantly treated with ICS in the early phase III trials showed a significant incremental effect of roflumilast on both exacerbations and lung function.[127] Given the presence of a (relative) corticosteroid resistance in COPD, mainly caused by the reduction of HDAC2 activity by oxidative stress,[130] it seems logical that restoring the HDAC2 activity with PDE inhibitors, phosphoinositide-3 kinase-delta (PI3Kδ) inhibitors and macrolides could reverse the corticosteroid resistance and result in synergistic activity.[130]

So far, roflumilast (Daxas® (Europe), Daliresp™ (USA)) has been approved in several countries including the European Union (EU), USA and Canada. Presently, roflumilast (500 μg once daily) is recommended for COPD stages III and IV with a history of chronic bronchitis and frequent exacerbations as add-on therapy.[6]

Targeting other PDE isoenzymes (combinations) for application in chronic inflammatory airway disease is presently being studied. PDE3 inhibition produces bronchodilation.[131] Future studies with combined PDE3/4 inhibitors should demonstrate their putative effectivity in asthma and COPD.[132]

Anti-IgE

Immunoglobulin E (IgE) plays a pivotal role in the allergic inflammation and mediates its effects through binding to a high affinity IgE receptor (FcεRI), primarily found on mast cells, basophils and dendritic cells. Alternatively, IgE may be linked to a low affinity receptor (FcεRII, CD23) on T cells, B cells and monocytes.[133] Cross-linking of the FcεRI receptor causes the release of a number of potent inflammatory mediators, while the low-affinity receptor is mainly involved in regulation of the immune response. Several studies have shown a close relationship between increased serum IgE levels and the prevalence of bronchial hyperresponsiveness and/or asthma.[134]

Omalizumab is a humanised, monoclonal IgG1 antibody (moAb) directed to the site of the Fc portion of free IgE, thus preventing the interaction with the human IgE receptors and the subsequent IgE-facilitated allergen uptake and inflammation. Applying total serum IgE (combined with body weight) for dose selection and frequency makes omalizumab the first asthma treatment based on a biomarker approach. In a large number of studies in both adult and paediatric patients with moderate to severe persistent allergic asthma, omalizumab (subcutaneously every two to four weeks) effectively reduced serum IgE levels resulting in sustained improvements in disease control and quality of life (see Di Domenico et al., and the references therein).[135] Apart from allergic asthma, omalizumab showed clinical efficacy in several other IgE-driven conditions including rhinosinusitis, conjunctivitis and bronchopulmonary allergic aspergillosis.[136]

Omalizumab (Xolair®) was first registered in Australia (2002) and subsequently in most countries worldwide. Its clinical indications and applications for persistent allergic asthma vary between countries, largely driven by economic factors. Substantial treatment efficacy is achieved in approximately one third of the patients, while one third show little or no response. Presently, it is unknown what distinguishes responders from non-responders and hence, efficacy should be evaluated after an initial trial of 16 weeks (see Di Domenico et al., and the references therein).[135] The most currently reported side effects ascribed to omalizumab include local symptoms (pain, bruising), while anaphylaxis has been reported in up to 0.2% and may occur within 24 hours of injection.[137]

Current guidelines recommend omalizumab as add-on therapy in step 5 for the treatment of patients (≥12 years) with moderate to severe persistent allergic asthma, with or without concomitant allergic rhinitis, uncontrolled despite optimal pharmacological treatment in combination with appropriate allergen avoidance.[1,31] Recent evidence also suggests some efficacy in non-allergic asthma,[138] which is in line with previous observations but requires further exploration. Another potential application includes combined use of the anti-IgE moAb with allergen-specific immune therapy for increased safety and efficacy.[139] Presently, developments to improve the efficacy of anti-IgE approaches are ongoing (see Holgate and the references therein).[22].

Anti-cytokines

Several cytokines have been implicated in the inflammatory cascades within the different asthma and COPD phenotypes. Some cytokines are disease enhancers while others attenuate the disease.[140] The cytokine network is complex and includes a substantial overlap and redundancy. Th2-pathway derived cytokines, including IL-4, IL-5 and IL-13, play an important role in allergic asthma associated with eosinophilic airway inflammation,

while e.g. TNF-α prevails in severe persistent asthma and COPD characterised by airway neutrophilia is linked to corticosteroid refractoriness.

In the last decade, an increasing number of anti-cytokine approaches have been explored, but so far, none of these strategies have fulfilled the criteria of clinical applicability.[22]

Interestingly, after initial conflicting results in allergic asthma,[22,141] the anti-IL-5 moAb mepolizumab (750 mg i.v. monthly), showed treatment efficacy in patients with severe refractory asthma with persistent sputum eosinophilia by significantly reducing the number of exacerbations along with improvement of other asthma endpoints and by allowing their oral corticosteroids to be tapered off.[142,143] Large clinical trials testing anti-IL-5 approaches in severe persistent asthma are presently ongoing and should provide a conclusive answer on this treatment strategy in this disease subset.[22]

Other novel cytokine targets include IL-9, IL-13, IL-17, IL-25 and thymic stromal lymphopoietin. Presently, an increasing number of approaches directed against these cytokines are being tested in several clinical trials of severe persistent asthma.[22,140]

Apart from offering an innovative treatment approach, anti-cytokine therapy has several drawbacks: (often) a limited efficacy as a result of substantial overlap within the inflammatory cascade, potentially hazardous side effects in the case of more upstream or multi-functional targets and high production costs. Perhaps targeting more than one (downstream) cytokine pathway can offer sufficient treatment efficacy along with an acceptable safety. In addition, more cost-effective antibody production strategies include peptide-based vaccination or the induction of neutralising antibodies requiring lower doses.[144,145]

Future treatment strategies

Treatment options for asthma and COPD are evolving rapidly with the increasing insight into the basic mechanisms of both disorders. Several biologicals directed against different components of the airway inflammation, currently in various clinical stages, are expected to offer alternative treatment options for patients unresponsive to conventional therapies. CRTH2 (chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells) blockade represents a novel upstream anti-inflammatory approach that may provide an alternative to inhaled corticosteroids. Presently, many orally active CRTH2 receptor antagonists are in various clinical development stages and the first results in (eosinophilic) asthma appeared promising.[146,147]

Furthermore, approaches targeting disease-related mechanisms other than the airway inflammatory process have been proposed. In particular, preventive strategies aimed at increasing airway resistance to environmental insults and their subsequent interaction with the airway epithelium may have sustained clinical efficacy.[22] Alternatively, prenatal factors shaping pro-asthmatic phenotypes could help to identify critical pathways for customised therapy.[22] Modulation of various (patho)physiological processes, including lung ageing,[148,149] tissue repair,[150] proteolysis,[151] airway smooth muscle hyperproliferation[152] and fibrosis[153] could also contribute to future treatment options. To date, there have been several advances in anti-infective and anti-oxidant approaches to supplement existing treatments of asthma and COPD, especially, addressing mechanisms which suppress inflammatory genes – independently of HDAC2 - thereby dealing with corticosteroid insensitivity in certain phenotypes.[154] Targeting cell signalling pathways and transcription factors by inhibition of e.g. p38 mitogen-activated protein kinase (p38 MAP-kinase), nuclear factor-kappaB (NFκB), inhibitory factor-kappaB kinase (IKK-2) or phosphoinositol-3-kinase (PI3K) δ may offer potentially effective treatment alternatives, although systemic inhibition of these ubiquitous molecules is anticipated to induce serious side effects, which precludes their systemic application.[155-158] The majority of these novel treatment strategies are in preclinical phase and await clinical validation.

SUMMARY

Both asthma and COPD are highly heterogenic, chronic inflammatory airway diseases.[159] Although corticosteroids, often combined with long-acting bronchodilators, represent the mainstay pharmacotherapy in milder disease, they are much less effective in severe persistent asthma and COPD. In addition, ICS do not cure any of these conditions. So far, targeted approaches through anti-mediator drugs, including leukotriene modulators and selective PDE4 inhibitors, have shown clinical efficacy in specified disease phenotypes only. Biologicals, except for anti-IgE, so far, have not met the general expectations in clinical studies as predicted from animal models and human in vitro tests. As part of future customised treatment strategies, accurate phenotyping should help to identify key (inflammatory) components within a certain disease subset both as targets and for monitoring of innovative therapies. The evidence of asthma and COPD as potentially systemic conditions calls for the development of systemically active drugs without intolerable side effects. Overall, integrated approaches may be needed to combat the conditions at a more multifaceted level, potentially implying combinations of different treatment strategies.

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REVIEW

Management of encapsulating peritoneal sclerosis: a guideline on optimal and uniform treatment

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ABSTRACT

Encapsulating peritoneal sclerosis (EPS) represents a rare complication of long-term peritoneal dialysis (PD). It is characterised by diffuse peritoneal membrane fibrosis, progressive intestinal encapsulation and the clinical spectrum of intestinal obstruction. The pathogenesis is as yet not well understood but includes inflammation, angiogenesis and fibrosis. The current diagnosis of EPS lacks specificity and relies on clinical, radiographic or macroscopic evaluation. There is no general agreement on managing EPS although accumulating clinical data suggest drug treatment (steroids, tamoxifen), surgery (enterolysis) or a combination of both. Here, we provide a short overview on the current knowledge of EPS, with a focus on treatment. Moreover, we present a diagnostic and a therapeutic algorithm for EPS based on the best available published data and our combined experience.

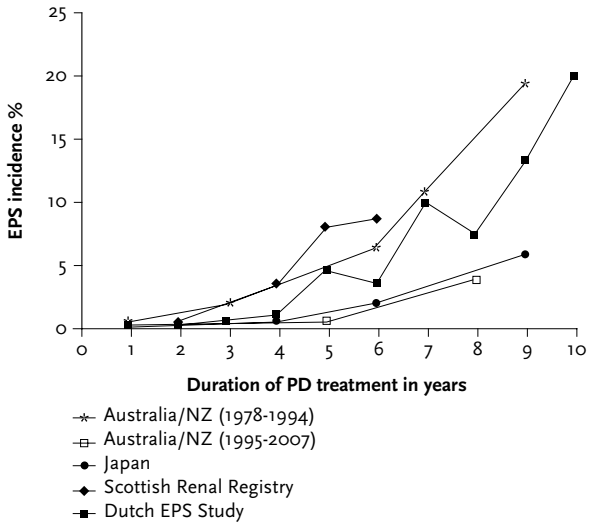
KEYWORDS

Encapsulating peritoneal sclerosis, enterolysis, immune suppressive, management algorithm, peritoneal dialysis

INTRODUCTION

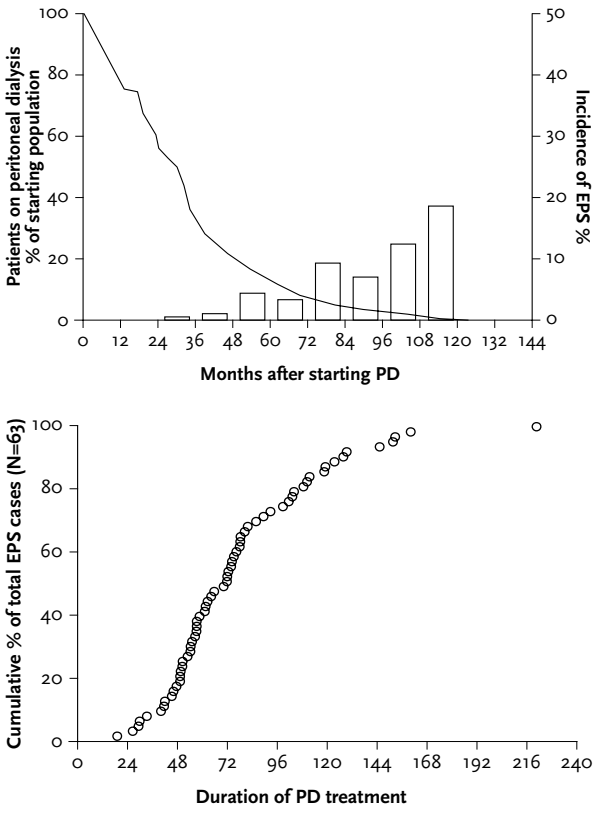
Encapsulating peritoneal sclerosis (EPS) complicating peritoneal dialysis (PD) is a rare disease of the peritoneum characterised by the presence of an inflammatory and fibrotic peritoneal capsule, which partially or completely entraps the bowel.[1] The reported prevalence of EPS within the PD patient population ranges worldwide from 0.7 to 3.7%.[2-5] The time on PD is the most important risk factor for EPS, possibly because it represents the time the peritoneum is exposed to the potential harmful effects of dialysis fluids.[4] Other possible factors associated with the development of EPS include age at the start PD, number of peritonitis episodes, fast peritoneal membrane transporter status, loss of ultrafiltration, and kidney transplantation.[6,7] Within the first few years of PD treatment, the incidence of EPS is usually less than 1%, but rises significantly after two to three years exceeding 15% in the group of patients on PD for ten years or more (*figure 1*). The overall number of patients on PD rapidly decreases within the first years after starting PD and after three years only 25% of the original cohort were treated with PD (*figure 2*). Still, over 90% of all EPS cases are treated with PD for more than three years (*figure 2*). Unfortunately, the early stages of EPS are difficult to recognise although progressive loss of

Figure 1. *The incidence of encapsulating peritoneal sclerosis (EPS) in relation to duration of peritoneal dialysis (PD) treatment. The EPS incidence is not cumulatively shown and should be interpreted as the percentage of patients diagnosed with EPS within the population of patients treated with PD for a given number of years (shown on the x-axis)*



Data from Australia/New Zealand for two time periods (Rigby, 1998 and Johnson, 2010),[2,5] Japan (Kawanishi, 2004),[3] Scotland (Brown, 2009),[32] the Netherlands (Korte, 2011)[7] are shown.

Figure 2. *The top figure shows the percentage of patients who remain on peritoneal dialysis (PD) after starting treatment (black line, total number patients 126). The bars show the incidence of encapsulating peritoneal sclerosis (EPS) as the percentage of patients diagnosed with EPS within the population of patients treated with PD for a given number of months (shown on the x-axis). The bottom figure shows the cumulative percentage of EPS patients in relation to their time of treatment with PD*



All data were obtained from the Dutch EPS study (Korte, 2011)[7].

ultrafiltration is frequently observed in patients who go on to develop EPS.[8,9] The consequences of EPS are devastating and mortality rates exceed 50%, most commonly because of complications related to persistent bowel obstruction (e.g. perforation) and prolonged parenteral feeding.[2,5,10] Most cases of EPS (>50%) are reported after PD treatment has been stopped either because of symptoms of EPS, a non-resolving peritonitis, or kidney transplantation.[3,7] The last-mentioned condition is coined post-transplantation EPS and has been described as a novel entity.[11,12] Post-transplantation EPS has a major negative impact on patient survival after kidney transplantation and EPS-related mortality is the fourth known cause of death in this patient population.[13]

Timely diagnosis and treatment of EPS seems warranted as it may offer the opportunity for resolving the bowel obstruction at an early stage, before complete encapsulation has occurred. Unfortunately, there is much uncertainty and delay in establishing the diagnosis of EPS. Furthermore, there is a lack of consensus on best therapeutic options to guide the management of EPS.

The Dutch EPS registry was successfully launched in June 2009 and is currently collecting clinical data as well as related biological patient material of cases with a possible or definite diagnosis of EPS. It is a collaboration of the Dutch kidney centres and the Hans Mak Institute.[14] Also an expanding international collaboration with the UK registry and other European countries has been established recently.[15] The main goal of the registry is to track the routine clinical outcomes of patients with EPS and contribute to a better medical understanding of the disease. The present article provides a short overview of the current knowledge on EPS, with a focus on treatment. We outline a rational strategy that can be used to guide the diagnosis and treatment of patients with EPS.

PATHOGENESIS

Appreciating the current knowledge on the mechanisms that lead to EPS is essential for the development of a management approach.

EPS can be considered an inflammatory repairing response of the peritoneum that has been damaged by chronic exposure to bio-incompatible dialysis fluids.[16,17] In an attempt to create a comprehensive overview of the disease, Kawanishi classified the disease into different stages.[18] In the early stages of EPS, the thin encapsulating membrane shows active inflammation. This is followed by elaboration of a thickened fibrotic membrane that progressively impairs normal bowel movement. Eventually, the inflammation subsides and a thick acellular fibrotic membrane remains that encloses the intestines.[19] During PD treatment the peritoneal changes include submesothelial thickening and fibrosis, accompanied with neoangiogenesis.[20] A key pathological mechanism may be the epithelial to mesenchymal transition (EMT) of mesothelial cells (MC). In this process, new fibroblast cells arise from local conversion of MC by EMT.[21,22] Although it is as yet unclear to what extent EMT is also present in EPS development, TGF-beta is one of the central regulators.[23] Other growth factors and molecules may also play a role in the development of EPS. In an experimental model of EPS, it was for instance noted that vascular endothelial growth factor is important in the EPS-like changes of the peritoneal membrane.[24]

EPS usually develops after long-term PD, but not all long-term PD patients will necessarily develop EPS. Which factors cause or allow its development is not exactly known but a second hit may be an important trigger. The 'two-hit theory' hypothesises that the preconditioned thickened and transformed peritoneum undergoes a second hit triggering symptomatic EPS.[25] This second event may be peritonitis, transplantation, or discontinuation of PD.[1,26]

DIAGNOSIS

The diagnosis of EPS lacks specificity but should include the clinical spectrum of intestinal obstruction with or without the existence of inflammation parameters and the presence of peritoneal sclerosis confirmed by macroscopic inspection or radiological findings.[27] The appearance of ultrafiltration failure, bloody ascites and elevated markers of inflammation such as C-reactive protein (CRP) may express the early inflammatory nature of the disease.[18] Unfortunately, in most cases EPS is diagnosed when abdominal pain due to recurrent or chronic bowel obstruction becomes clinical manifest.[28,29] Physical examination may indicate the presence of ascites or ileus in the abdomen. In some instances a palpable abdominal mass is found.[30] As none of these findings are specific, other diagnoses such as infections, tuberculosis, pancreatitis and malignancies (e.g. lymphoma) should be ruled out.

The provisional diagnosis of EPS is usually made after radiographic evaluation by CT scan showing a characteristic picture of a thickened peritoneum encapsulating the intestines.[31-33]

In case of clinical suspicion and a negative CT scan, diagnostic surgery (laparoscopy or laparotomy) can provide the diagnosis.[25,34] It also facilitates taking peritoneal biopsies to detect early EPS or exclude other causes.[35] However, surgical exploration is a challenging decision as extensive peritoneal fibrosis and bowel loops adherent to each other may exist.[1] Therefore, we advocate performing timely diagnostic surgery to establish the diagnosis of EPS with certainty.

TREATMENT

Cessation of PD treatment

An important initial step in the management of EPS is cessation of PD to prevent further peritoneal damage.[27,36,37] Although this approach seems reasonable, it is a matter of debate as this approach does not always reverse the progression of peritoneal fibrosis.[38] A logical explanation might be the absence of peritoneal lavage to remove fibrin, profibrotic factors and cytokines. Studies show that more than half of EPS cases are often diagnosed two years after stopping peritoneal dialysis and less severe cases of EPS may even worsen after discontinuation of PD.[3,32,39] Leaving the catheter in situ and performing regular peritoneal lavage in patients who have discontinued PD has been tried in Japan. However, no convincing evidence of a beneficial effect on the course of EPS has been reported yet.[3,40,41]

A clear statement on withdrawing patients from PD after the diagnosis of EPS has been established may be difficult. But given the association between PD duration and progression of EPS we propose a switch from PD to haemodialysis with removal of the PD catheter.

Immune suppressive medication

There is no agreement on the use of immune suppressive drugs to treat EPS. This is largely due to a lack of targeted pharmacological therapies and absence of trials with a significant number of patients. Immunosuppressants such as azathioprine, myocophenolate mofetil and sirolimus have been used in patients with EPS, usually co-administered with corticosteroids.[42-44] But the available data are limited to anecdotal reports and the superiority of these drugs to corticosteroids alone is not proven. Here we summarise the two best-documented management strategies for EPS, corticosteroids and tamoxifen. We propose an algorithm which is based on a critical appraisal of published data and our combined experience.

Corticosteroids

Corticosteroids are the most reported and successfully used drugs in treating EPS. Steroids are thought to

be effective in suppressing the inflammatory process of the peritoneal membrane and inhibiting collagen synthesis and maturation.[45] Thickening of the peritoneal membrane may even disappear. In Japan, the use of corticosteroids as first-line therapy has gained widespread acceptance. In a report by Kuriyama *et al.* all patients treated with corticosteroids maintained good prognosis after the diagnosis of EPS. Patients who did not receive corticosteroid therapy died within eight months of diagnosis.[46] Similarly, others have reported lifesaving treatment with corticosteroid therapy.[40,44,47-49] Only one series has reported a clinical improvement rate of 38.5% in patients treated with corticosteroids alone.[3]

Importantly, the use of immune suppressive medication only seems appropriate in case of ongoing inflammation. Albeit aspecific, this can only be assessed by clinical observation of the patient's status and laboratory measurements of levels of inflammatory biomarkers, such as CRP.[18,48,50] In the late stages of EPS, surgery may be more effective as the inflammatory tissue seems to be gradually replaced by fibrosis and is less likely to shrink with medical therapy.[18] However, there are no data to support this view and in our experience almost all patients are inflammatory to some degree.

Although the optimum dose and duration of steroid therapy have not been established by a controlled trial, most publications support a regimen of prednisolone 0.5 to 1.0 mg/kg/day or a pulse dose of 500 to 1000 mg methylprednisolone for two to three days.[3,25,46,47,51,52] The dose of prednisolone needs to be approximately 0.5 to 1.0 mg/kg/day during the first month, 0.25 to 0.5 mg at months 2 and 3 and thereafter tapered to 10 mg at six months. Treatment with steroids must be continued for at least one year. It is important to prolong the period of high-dose steroids in a responding patient with a persistently elevated CRP level as dose reduction may result in recurrence of intestinal obstruction and inflammation, responding to retreatment with prednisolone.[48] Of course, the well-known potential adverse effects of prednisolone should be taken into account but the high mortality of EPS tips the balance in most cases in favour of treatment. Peritonitis, particularly caused by tuberculosis, should be ruled out as far as possible.[53] Any sudden rise in CRP level not adequately responding to steroids should raise the suspicion of a bacterial peritonitis because of spontaneous small bowel perforation.

Tamoxifen

Tamoxifen is a selective oestrogen receptor modulator (SERM), which has been successfully used in fibrosclerotic disorders such as fibrosing mediastinitis, sclerosing cervicitis, desmoid tumours, retroperitoneal fibrosis, and Dupuytren's contracture.[54-57] In recent years, the use of tamoxifen in the treatment EPS patients has gained more interest. Allaria *et al.* were the first to describe the successful use of tamoxifen in an EPS patient.[58] The therapeutic potential of tamoxifen therapy is also confirmed in a significant proportion of other reported cases. Most reports show improvement of the intestinal function and a decrease in inflammation and fibrosis.[59-61]

The largest controlled series by the Dutch EPS study showed a decreased mortality in a group of EPS patients treated with tamoxifen (45.8 *vs* 74.4%, p=0.03) compared with a group who were not.[62] Remarkably, a large case series from the UK showed no improvement in survival rate when tamoxifen was used.[63] This discrepancy in survival outcomes may be the result of including more severe cases in the Dutch study.

Although the specific working mechanism of tamoxifen remains to be defined, it appears different from the treatment of breast cancer. In the latter, its main action is through binding of active metabolites to the oestrogen receptor (ER).[64] Inhibition and modulation of TGF-beta, which are ER-independent pathways might be the rationale behind the positive results in fibrotic diseases.[65] Interestingly this was underlined by findings from a recent study by Braun *et al.* showing almost no ER expression in the peritoneal tissue of EPS patients.[66]

Tamoxifen is an alternative to the (long-term) use of corticosteroids as its side effects are mild compared with prednisolone. When remission on corticosteroids is absent additional tamoxifen can be considered. Alternatively, when there is doubt of an underlying inflammatory EPS, tamoxifen may be considered to be first choice. Unfortunately no data exist to support this view as there are no comparative studies for tamoxifen and corticosteroids, and tamoxifen is nearly always given in combination with steroids. In the Dutch EPS study, the multivariate analysis with adjustment for concomitant prednisone use in the tamoxifen-treated group confirmed the trend of improved survival.

Most studies in EPS report a tamoxifen dose between 20 and 40 mg/day.[59,60,67-70] This is similar to that used in retroperitoneal fibrosis.[56,71] After the introduction of tamoxifen therapy, favourable clinical outcomes are often seen within two to six months.[51,58,67,69] When there is clinical improvement the treatment with tamoxifen is probably maintained for a longer period analogous to recommendations on retroperitoneal fibrosis.[56] We recommend an initial dose of 20 mg twice daily for at least one year. The CT scan can be used to monitor resolution of peritoneal thickening and fluid collection after tamoxifen therapy.[59] Tamoxifen may have beneficial effects in the management of EPS but caution is warranted and more studies are needed to confirm its (adverse) effects. In addition, the adverse effects of tamoxifen such as strokes, thromboembolic events, hot flushes, and endometrial carcinoma have to be considered carefully

for each patient.[72,73] Reported adverse effects of tamoxifen in the EPS literature include arteriovenous access thrombosis, pulmonary embolism, thrombopenia, and calciphylaxis.[59,52,60]

Surgery

Surgical treatment has created exciting possibilities in the management of EPS. New surgical techniques have gained broad attention and nowadays even specialised referral centres for surgery have been established in the UK.[74]

In the past, mortality rate as a result of surgical complications was high and prognosis post-surgery was poor.[75,76] The new surgical technique of enterolysis has shown to be successful in treating more than 92% out of 130 EPS patients with a postsurgical mortality of 6.9%.[77] The procedure of enterolysis implies the ablation of fibrotic tissue and lysis of the adhesions.[25] Of note, a peritonectomy as part of the surgical approach in EPS has been used in Manchester, but no large-scale studies have been published yet.[74]

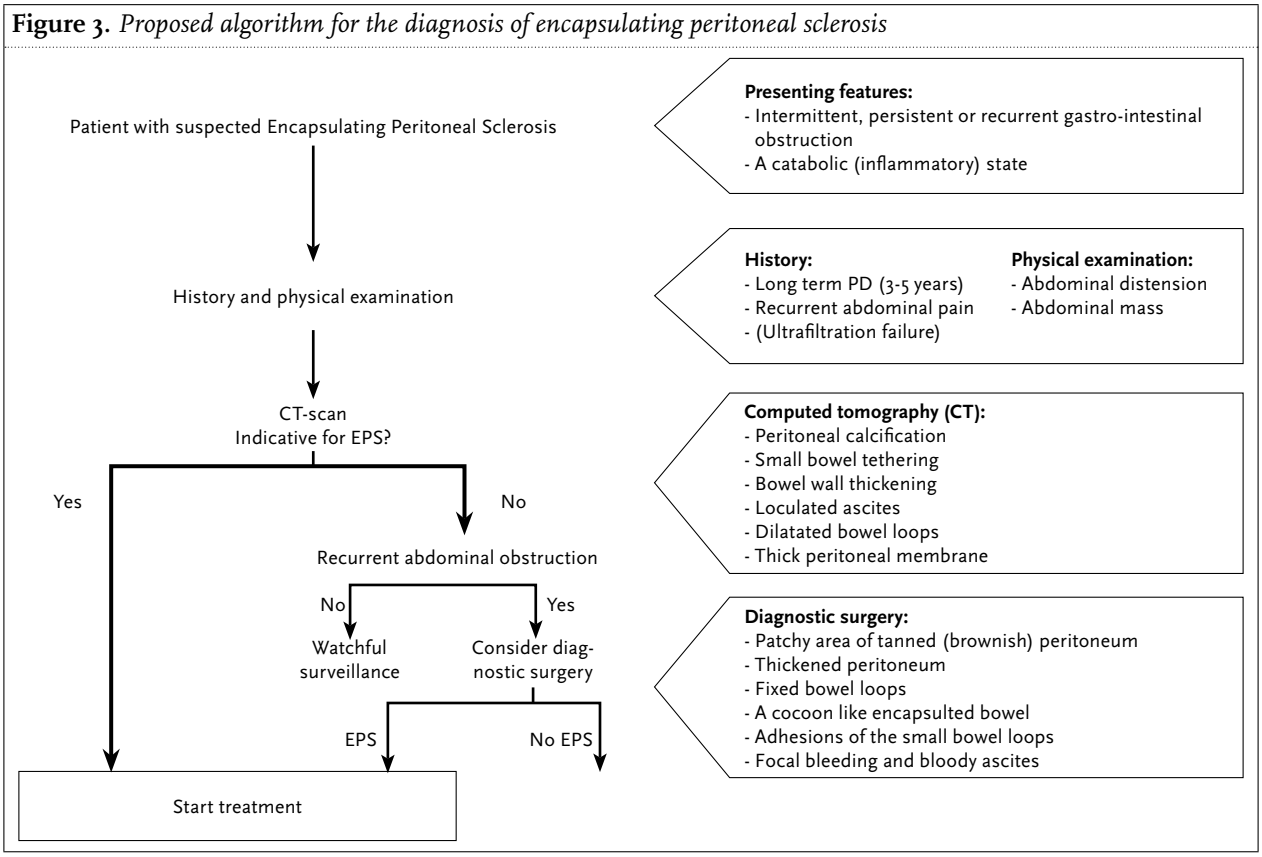
The surgical procedure to remove the adhesive lesion may be extremely time consuming, demanding and very hazardous. It is proposed that surgery should be performed if the patient does not get better with conservative or medical therapies.[78] Surgery is indicated after the inflammation has subsided and if ileus symptoms become pervasive.[18] Sometimes the encapsulation is very localised and in these cases, it tends to be at the ileocecal part of the intestines.[79,80] These EPS patients benefit most from a relatively easy to perform localised peritonectomy.

Some complications after surgical intervention include recurrent intestinal obstruction, formation of fistulas, or sepsis due to a perforated intestinal wall.[30] In addition, surgery may not always exclude the recurrence of adhesions or symptoms of bowel obstruction. In a report by Kawanishi *et al.* 33 (25%) of the 130 patients required re-surgery.[81] In order to prevent re-obstruction, suturing intestine to intestine as part of the Noble procedure has been described and also postoperative prophylaxis with steroids or tamoxifen might be useful.[77]

Nutritional management: total parenteral nutrition

The decision on planning patients for nutritional support is necessary to prevent malnutrition as this is a major problem in EPS.[39] A study from the UK has highlighted the importance of total parenteral nutrition (TPN) and dietary counselling in the integral approach of EPS. In a group of EPS patients undergoing surgery, improved surgical outcomes were reported when TPN was used as part of the preoperative care.[82] The authors recommend careful monitoring of the nutritional status by use of markers such as albumin. With regard to this statement, we would like to

Figure 3. *Proposed algorithm for the diagnosis of encapsulating peritoneal sclerosis*



underline the negative correlation between inflammation and markers such as albumin.[83]

However, TPN is not a curative therapy as low recovery rates are observed when it is used alone.[3,78] The Pan Thames study also observed shorter time to death (10 months, range 0 to 101) in the TPN treatment group compared with patients maintained on oral nutrition (15 months, range 0 to 119).[63] Although there was no information on the initial nutritional status or clinical condition of patients the difference in survival could be due to TPN-related complications such as infections.[84]

CONCLUDING REMARKS

EPS is an infrequent but severe complication of PD with the incidence increasing progressively with the duration of dialysis. A high degree of suspicion for EPS in any (former) PD patient with signs of bowel obstruction is warranted. Given the current published data and our experience with EPS cases, there is a rationale for corticosteroids, tamoxifen and surgery in the treatment of EPS. Integrating the available data, we have developed algorithms for the diagnosis and treatment of EPS (*figure 3* and *4*).

A multidisciplinary approach to the patient with EPS is needed and should at least involve a nephrologist, dietician and surgeon. In addition, a specialised surgical centre or surgeon is needed in the Netherlands to ensure a high standard of quality for this challenging and time-consuming abdominal surgery in EPS patients. Studies on the complex pathogenesis and the role of inflammatory-mediated mechanisms are needed and may provide new clues for treatment. Finally, the optimum dose and duration of steroid therapy and the benefits of tamoxifen need to be further investigated.

We encourage physicians to submit every suspected or proven case of EPS to the Dutch EPS registry at www.epsregistry.eu.

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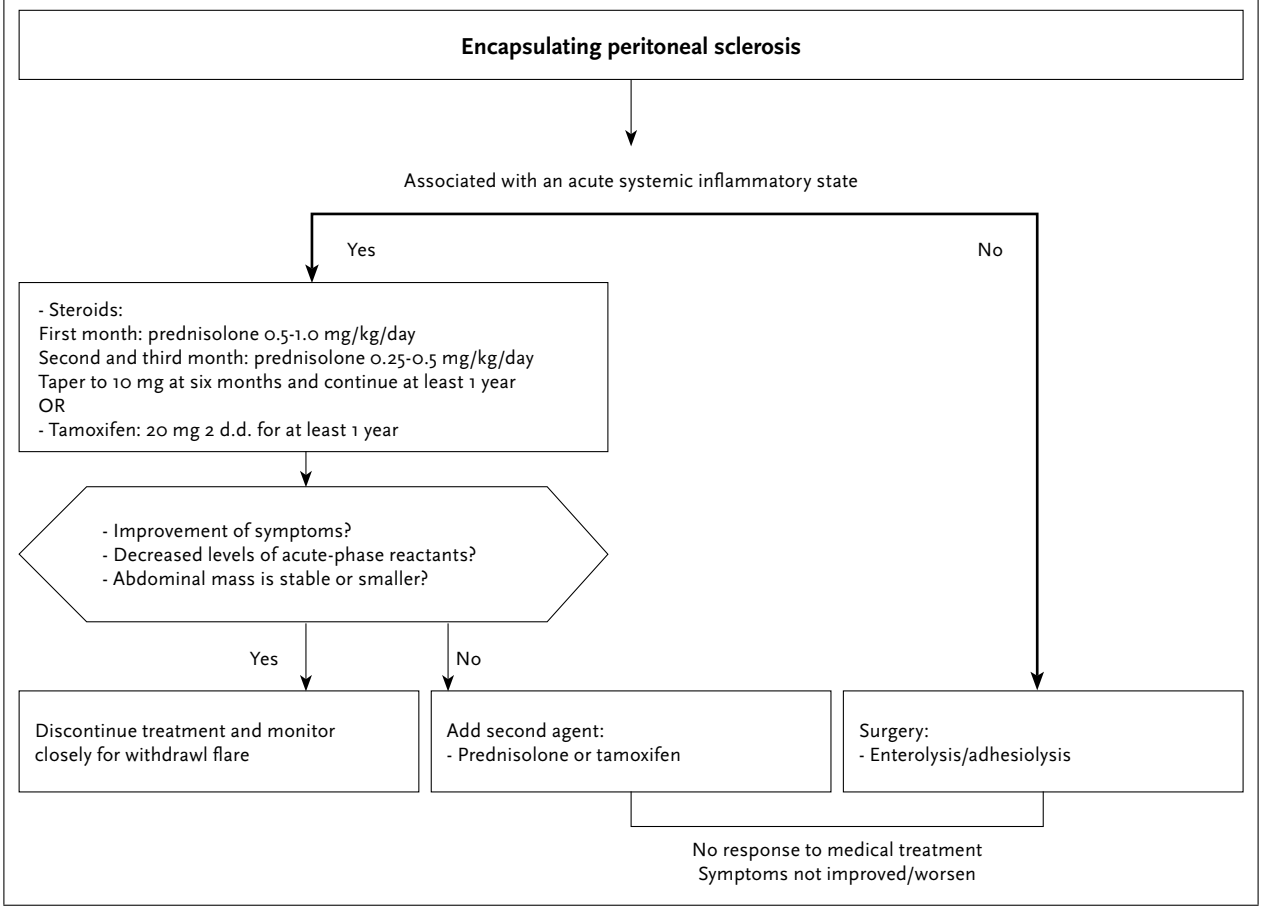
Figure 4. *Proposed algorithm for the treatment of encapsulating peritoneal sclerosis*



the EPS registry include: E. Steyerberg and H. Lingsma, Epidemiology, Erasmus MC, Rotterdam. The EPS Registry is supported by the Hans Mak Institute.

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ORIGINAL ARTICLE

Quantitative HBV DNA and AST are strong predictors for survival after HCC detection in chronic HBV patients

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ABSTRACT

Hepatitis B virus infection (HBV) is an important co-factor in the development of hepatocellular carcinoma (HCC). We studied whether quantitative HBV DNA at time of HCC detection influences survival of HCC patients.

All diagnosed HCC cases between 2000 and 2008 at our university-based reference centre were analysed to determine the influence of hepatitis B viral load on overall survival. Clinical and virological findings were evaluated in univariate and multivariate analyses, survival rates were assessed for HCC patients with a high viral load (HBV DNA ≥10^5 copies/ml) and low viral load (HBV DNA <10^5 copies/ml).

HCC was diagnosed in 597 patients, including 98 patients with HBV. The group of 37 patients (38%) who had a high viral load contained more HBeAg-positive patients, had lower serum albumin levels and higher serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The one- and five-year survival rates of HCC patients with a high viral load were 58% and 11% and for HCC patients with a low viral load 70% and 35%, respectively. In multivariate analysis a higher AST level and higher viral load were significantly associated with shorter overall survival (HR=2.30; p=0.018, HR=1.22; p=0.015, respectively).

HBeAg positivity, low albumin level or high AST or ALT levels in HCC patients are associated with a higher HBV DNA. HBV DNA level at detection is associated with overall survival of HCC patients. These findings support the concept that after HCC detection adequate suppression of HBV DNA by nucleoside analogue therapy may improve survival.

KEYWORDS

HBV DNA, hepatitis B virus (HBV), hepatocellular carcinoma (HCC), survival, viral load

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer-related mortality.[1] In many patients, HCC occurs against the background of a chronic viral infection. Chronic hepatitis B virus (HBV) infection, chronic hepatitis C viral (HCV) infection and cirrhosis are major aetiologies of HCC.[2,3] Worldwide approximately 400 million people are chronically infected with HBV.[4]

In the last 15 years, reliable quantification of HBV DNA over a large dynamic range has become feasible. Several hospital-based and community-based studies have subsequently found significant associations between the level of serum HBV DNA and the risk to develop liver cirrhosis or HCC.[5] After an HCC has developed and surgery is performed, recurrence of HCC is associated with original tumour size, number of tumours, grade of differentiation, level of alpha-fetoprotein (AFP), alcohol consumption and HCV co-infection.[6-9]

The impact of viral load on survival of HCC patients after surgery with curative intent may be overshadowed by tumour-related factors or stage of the liver disease at detection of HCC. Understanding the respective role of tumour and viral factors in HCC survival may provoke new treatment strategies to increase HCC survival. It has been hypothesised that anti-viral therapy for HCC patients with

active HBV replication along with HCC treatment might reduce the recurrence rates for HBV-associated HCC.[10]
A few recent studies have evaluated HBV replication status as a predictor of HCC recurrence.[9,11,12] However, to our knowledge only a few reports from high endemic areas published to date, often with a limited number of patients, have suggested a relation between viral status and prognosis in patients with HBV-associated HCC.[13-16] In the current study in a low endemic area, univariate and multivariate analyses of the prognostic factors, including serum HBV DNA level, were performed to determine whether the HBV DNA levels at the time of HCC appearance are associated with overall survival.

MATERIAL AND METHODS

Study design

A hospital-wide registry, including data from patient files and virological records of all patients diagnosed with HCC at the Erasmus MC in Rotterdam, the Netherlands during the period from 1 January 2000 to 31 December 2008, was used. The diagnosis of HCC was made from radiological and biochemical findings and, if necessary, confirmed by histological examination. Within the group of nodules larger than 2 cm, with the typical features of HCC on a dynamic imaging technique, no biopsy was performed. Nodules between 1-2 cm were investigated further with two dynamic studies imaging modalities, computed tomography (CT) scan or magnetic resonance imaging (MRI) with contrast. If the appearances were typical of HCC (i.e., hypervascular with washout in the portal/venous phase) in two techniques the lesion was treated as HCC. If the findings were not characteristic or the vascular profile was not coincidental among techniques, the lesion was biopsied, according to the AASLD guidelines.[17]
All HBsAg(+) patients were included in this study. Follow-up of HCC recurrence by an alpha-fetoprotein (AFP) test and ultrasound, CT, or MRI was done every three to six months for up to two years after potential curative treatment. After two years, follow-up was continued annually for up to five years after treatment. Recurrence of tumour in the treated area or elsewhere was defined as re-appearance of vascular enhancement.[17] In the presence of underlying liver cirrhosis, lifetime follow-up was performed. If HCC recurred, the size, number, and localisation of the recurrent disease were registered. Verification of living patients was done using information obtained from the general physician or the civil registration.

Biochemical and serological markers

Data were collected on patient age, gender, nucleotide or nucleoside analogue therapy (lamivudine, adefovir, telbuvidine, tenofovir or entecavir or a combination of these drugs), AFP, size and number of lesions, and the presence of lymph node enlargement or metastases. The collected liver parameters included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and albumin. In addition, the Model For End-Stage Liver Disease (MELD) score was calculated. Cirrhosis was diagnosed using established clinical, biochemical, and histological criteria. Patients with cirrhosis were classified according to the Child-Pugh classification.
At time of HCC diagnosis, the serum HBV DNA level was assessed using in-house Taqman PCR (detection limit 400 copies/ml) based on the Eurohep standard, HBeAg (AxSYM, Abbott, Abbot Park, IL, USA) and hepatitis B surface antigen (HBsAg) (AxSYM, Abbott) status were measured.[18] A high HBV load was considered to be HBV DNA $\geq 10^5$ copies/ml, HBV DNA $<10^5$ copies/ml was considered a low viral load.[19] All patients were negative for anti-hepatitis C virus antibody and did not report alcohol abuse at time of diagnosis and commencement of this study.

Statistical analysis

Variables were compared using the Mann-Whitney U test, t-test or with the χ^2 test whenever appropriate. Statistical significance was considered if the p value was <0.05. Univariate analysis was used to assess the importance of prognostic factors on overall survival. Survival curves were drawn using the Kaplan-Meier method. The difference between Kaplan-Meier curves was tested using the log-rank test. The baseline characteristics age, gender, log bilirubin, log albumin, log AST, log ALT, log HBV DNA, log AFP, MELD score, Barcelona Clinic Liver Cancer (BCLC) score, HBeAg and anti-viral therapy were considered. Multivariate Cox regression analysis was performed with all characteristics with a p value <0.20 in univariate analysis and known factors associated with survival to determine the independent contribution of each variable. Analysis was performed using SPSS software.

RESULTS

Clinical, biochemical and virological data

A total of 597 patients were diagnosed with HCC. Out of these 597 patients, 98 patients (16%) fulfilled the inclusion criteria. The patient characteristics at presentation with HCC are shown in *table 1*. Median follow-up was 22 months (1-114). One year after presentation, 60% of the patients were still alive, and the five-year survival rate of this cohort was 21%. In 50 patients (51%), treatment with curative intent was initiated; this included surgical resection (wedge resection, segment resection, or hemihepatectomy), liver transplantation or radio

Table 1. *Patient characteristics at first presentation with HCC*

Characteristic	(n=98)
Age (years)*	55 (23-80)
Gender (male)	79 (81%)
Total bilirubin (µmol/l)*	18 (4-481)
Albumin (g/l)*	38 (22-49)
AST (U/l)*	69 (21-1278)
ALT (U/l)*	54 (19-670)
AFP (ng/ml)*	70 (1-652660)
MELD score*	6 (6-25)
Non-cirrhotic	22 (22%)
Child-Pugh classification	
A	49 (64%)
B	20 (26%)
C	7 (9%)
HBV DNA ≥10^5 copies/ml	37 (38%)
HBeAg‡	24 (25%)
Anti-viral (nucleoside or nucleotide analogue) therapy	50 (51%)
Number of tumours*	1 (1-7)
Tumour size (mm)*	34 (8-227)
Metastases	29 (30%)
BCLC	
Stage A	30 (31%)
Stage B	37 (38%)
Stage C	7 (7%)
Stage D	24 (24%)

AST = aspartate aminotransferase; ALT = alanine aminotransferase; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer score; *median (range); ‡ positive value.

Table 2. *Differences between patients with high and low HBV load*

Characteristic	HBV DNA <10.5 (n =61)	HBV DNA ≥10.5 (n=37)	p value
Age (year)*	56 (23-77)	54 (27-80)	0.650
Gender (male)	49 (80%)	30 (81%)	0.928
Total bilirubin (µmol/l)*	15 (4-481)	24 (6-372)	0.058
Albumin (g/l)*	39 (25-49)	35 (22-48)	0.032
AST (U/l)*	62 (21-328)	95 (33-1278)	0.002
ALT (U/l)*	50 (19-356)	67 (32-670)	0.039
AFP (ng/ml)*	70 (1-652660)	70 (2-121000)	0.640
Non-cirrhotic	15 (25%)	7 (19%)	0.516
MELD score*	6 (6-23)	7 (6-25)	0.253
HBeAg‡	11 (18%)	13 (35%)	0.047
Anti-viral (nucleotide or nucleoside analogue) therapy	32 (53%)	18 (49%)	0.716
Number of tumours*	1 (1-7)	1 (1-4)	1.000
Tumour size (mm)*	34 (8-200)	34 (11-227)	0.714
Metastases	15 (25%)	14 (38%)	0.166
BCLC			0.466
Stage A	21 (34%)	9 (24%)	
Stage B	23 (38%)	14 (38%)	
Stage C	5 (8%)	2 (5%)	
Stage D	12 (20%)	12 (32%)	

AST = aspartate aminotransferase; ALT = alanine aminotransferase; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer score; *median (range); ‡ positive value.

frequency ablation. In eight patients (8%) transarterial (chemo)embolisation (TACE) or another therapy such as radiotherapy or systemic chemotherapy with palliative intent was started. The remaining group of 40 patients (41%) received no therapy.

Fifty patients (51%) received oral anti-viral therapy. Nine patients had an increase of HBV DNA during the study period but none of these patients switched from the low HBV DNA group to the high HBV DNA group.

In 21 out of 50 patients (42%) a recurrence of HCC was documented after potentially curative treatment. The median time to recurrence was 12 (1-50) months. Recurrence of HCC presented as local recurrence in four patients (19%), a new lesion in 11 patients (52%) and metastases in six patients (29%).

Factors associated with HBV viral load

Among the 98 patients, 37 (38%) had a high viral load. As expected, the group of patients with a high viral load contained more HBeAg(+) patients, had a lower serum albumin level and had a higher serum AST, ALT, and total bilirubin level compared with the group of patients with a low viral load (*table 2*). Treatment with curative intent was not significantly different between patients with high and low viral load (p=0.188). Treatment of HCC was independent of the level of HBV DNA (p=0.202). Patients with a higher viral load more often had a recurrence of HCC after treatment with curative intent (p=0.025).

Univariate and multivariate analyses were performed to determine HBV-related predictors for overall survival (*table 3*). Multivariate Cox regression analysis was performed with all characteristics with a p value <0.20 in univariate analysis and known factors associated with survival to determine the independent contribution of each variable.

The strong correlation between AST and HBV DNA made it impossible to join them in one model. Separately, multivariate analysis confirmed both a high AST level and a high viral load (HBV DNA) to be significantly associated with a shorter survival (HR=2.30; p=0.018, HR=1.22; p=0.015, respectively). A higher AFP, a higher MELD score and a higher BCLC classification were also associated with a shorter survival (HR=1.30; p=0.008, HR=1.08; p=0.021, HR=1.95; p<0.001, respectively).

Association of serum HBV DNA levels at time of HCC diagnosis and overall survival

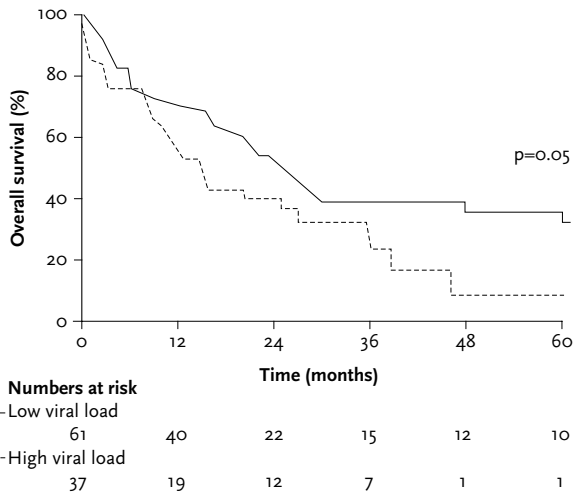
The median survival time of HCC patients with a high viral load was 15 months (1-62), and 25 months (1-114) in

Table 3. *Univariate analysis of factors associated with survival*

Variable	Hazard ratio (95% confidence limit)	p value
Age (10 years)	1.00 (0.78-1.27)	0.97
Gender (female:male)	0.80 (0.41-1.57)	0.50
log total bilirubin (10 µmol/l)*	1.02 (0.99-1.05)	0.31
log albumin (10g/l)*	0.68 (0.44-1.03)	0.07
log AST (U/l)*	2.30 (1.15-4.60)	*0.018*
log ALT (U/l)*	0.75 (0.31-1.80)	0.51
log AFP (ng/ml)*	1.32 (1.09-1.60)	*0.006*
MELD score	1.07 (1.01-1.14)	*0.033*
HBV DNA	1.22 (1.04-1.43)	*0.015*
HBeAg‡	1.47 (0.84-2.55)	0.19
Anti-viral (nucleotide or nucleoside analogue) therapy	0.69 (0.42-1.14)	0.15
BCLC	1.95 (1.54-2.48)	*<0.001*

AST = aspartate aminotransferase; ALT = alanine aminotransferase; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer score; *continuous value; ‡ positive value.

Figure 1. *Overall survival of HCC patients with high and low HBV DNA*



HCC patients with a low viral load (*figure 1*). The one-, three- and five-year survival rates of HCC patients with a high viral load were 58%, 32% and 11%, respectively. For HCC patients with a low viral load, the one-, three- and five-year survival rates were 70%, 39% and 35%, respectively (*figure 1*). Patients with higher serum HBV DNA levels at the time of tumour presentation had a shorter overall survival compared with patients with lower serum HBV DNA levels (p=0.05). Including HCC treatment into the total multivariate analysis, a high viral load continued to be significantly associated with a shorter survival (HR=1.18 (95% CL; 1.01 to 1.38); p=0.042).

DISCUSSION

In our study we showed in multivariate analysis that a high AST level and high viral load were two independent factors associated with poor survival. A unique and important finding of this study is that it demonstrates the impact of high viral load on overall survival of HCC patients despite the treatment they received. Consistently, we observed that biochemical profiles indicative of active inflammation in our data were worse in patients who had high viraemia than in patients who had low viraemia, further supporting the theory of the potential carcinogenic process through active inflammation associated with high viraemia.

Localised HCC tumours can be subjected to potentially curative treatments such as surgical resection, liver transplantation or radiofrequency ablation.[17] In our study 50 patients (51%) were able to receive treatment with curative intent. Only 8% of the study population received treatment with palliative intent; this low percentage is due to a limited availability of TACE treatment during the study period. Patients without treatment were often unable to receive treatment due to more advanced liver disease.

In many patients, HCC occurs against a background of advanced fibrosis or cirrhosis.[20-22] Cirrhosis decreases the regenerative capacity of the liver and therefore not every HCC patient is a suitable candidate for local surgical resection. Although many surgical and nonsurgical options have been developed for the treatment of HCC, the prognosis for these patients remains poor. Even in those who receive radical therapy, prevention of post-treatment recurrence remains a medical challenge.[23]

Several factors have been reported to be associated with poor survival after surgical resection or local ablation therapies, including tumour characteristics, such as multiplicity, size, AFP levels, portal invasion, surgical tumour findings, parameters related to liver function such as albumin levels, and Child-Pugh classification.[11,15]

Taking into account the fact that HCC arises in cirrhotic livers, evaluation of the detailed oncogenic process in patients with cirrhosis is an important subject for cancer prediction.[17]

Liver cirrhosis due to hepatitis C virus usually shows a rather steady and constant clinical course, which enables us to estimate the future carcinogenesis rate only from clinical information at the time of the diagnosis of cirrhosis.

However, in contrast to hepatitis C and other risk factors, it is known that HBV-related HCC is less associated with the presence of cirrhosis, and this trend becomes more obvious in younger patients often infected at birth whose duration of infection is not long enough to develop full-blown cirrhosis.[23] This observation has prompted the suggestion that HBV itself has direct carcinogenic potential.[23] The detailed mechanism of HBV-related liver carcinogenesis

is still unclear.[18,24] It is possible that active viral replication and HBx-protein expression contribute to the carcinogenic process.[11] Prospective studies have indicated a very strong correlation between the height of the viral load and the risk of developing HCC. Lamivudine therapy in patients with HBV-related compensated cirrhosis reduced the incidence of HCC in patients when viral suppression was sustained, but no previous report has studied the relationship of these viral factors and survival of HCC patients.[11,15,25,26]

When we investigate the relationship between hepatocellular carcinogenesis and its affecting and contributing factors, explanatory parameters should include not only tumour-related factors but also data on the extent of the liver disease, as e.g. included in the Child classification, BCLC and MELD classification. We also suggest including quantitative virological data in this prognostic modelling.

In the current study, patients with a higher viral load also had more elevated liver enzymes. Oral nucleoside or nucleotide analogue therapy has developed over the last years. The profile of drugs such as entecavir or tenofovir combines high efficacy with a low potential for resistance. Therefore, a logical next step is to treat all HBV-related HCC patients with nucleoside or nucleotide analogue therapy. A meta-analysis also suggested a potential efficacy of adjuvant interferon after curative therapy for HCC.[27] Two recent prospective studies focusing primarily on the correlation between hepatitis B viral load and recurrence of small HCC after curative resection revealed that HBV DNA level at resection was an important risk factor for recurrence of small HCC after surgery.[9,28]

A potential limitation of the present study is that the data were based on a retrospective cohort study. A large-scale prospective trial should be conducted in the future to elucidate the effect of sustained viraemia on survival of HCC patients and the prospective roles of antiviral treatment.

In theory, treating high viral load patients with antiviral drugs both pre- and post-operatively is reasonable. Current treatment in patients with advanced HCC is sorafenib, where median survival can increase by nearly three months.[29] In this study high HBV viral load and hepatic inflammatory activity were both significantly associated with a poor prognosis; median survival was ten months longer in HCC patients with a low viral load.[30]

Given the strong association between HBV viral load and overall survival, it is anticipated that the implementation of strategies for the use of antiviral therapy in this setting will result in a durable suppression of HBV replication and ultimately will lead to an increase of survival in HCC patients. We suggest that, for HCC patients with high serum HBV DNA levels, inhibition of viral replication may decrease inflammation and improve survival.

In conclusion, a lower albumin level or a higher serum AST or ALT activity are liver-related factors that are closely associated with a higher hepatitis B viral load. In our dataset as well as in the data of Qu et al. high HBV DNA shortened overall survival.[28] In the current analysis serum AST and viral load independently affected overall survival. This association supports the role for antiviral treatment for patients with a high HBV DNA together with treatment of HCC to increase overall survival. Further clinical trials with this endpoint are required to confirm the beneficial effect of hepatitis B viral suppression after HCC treatment to improve survival.

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None

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CASE REPORT

Fatal outcome of *Bacillus cereus* septicaemia

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ABSTRACT

Bacillus cereus is a ubiquitous environmental micro-organism which is often a contaminant of clinical cultures. Infections due to *B. cereus* are described, but mostly in immunocompromised patients. We report a fatal outcome of *B. cereus* septicaemia in an immunocompetent patient with a mechanical mitral valve.

KEYWORDS

Bacillus cereus, fatal outcome, fever of unknown origin, immunocompetent, septicaemia

What was known on this topic?
Bacillus cereus can cause deep-seated infections, such as endocarditis, in immunocompromised patients or intravenous drug users resulting in high morbidity and even mortality. In immunocompetent patients only cases of catheter-related infections have been published. These patients all fully recovered upon catheter removal and antibiotic therapy.

What does this add?
Our study adds that in immunocompetent patients with foreign body material the possibility of deep-seated infections must be carefully evaluated when *B. cereus* or other low pathogenic bacteria are cultured from blood. When a deep-seated infection is not considered in this patient group, this may result in premature discontinuation of antibiotic therapy, subsequent treatment failure and, as in our case, death. Furthermore, our study emphasises that in order to prove a deep-seated infection, early molecular comparison of bacterial strains retrieved from different samples may lead to the right diagnosis.

INTRODUCTION

Bacillus cereus is a ubiquitous environmental, gram-positive, facultative anaerobic, spore-forming rod, which is commonly considered a contaminant when cultured from clinical specimens. *Bacillus* species are commonly found in soil, dust, water, fomites and on mucous membranes of healthy people.[1,2] *B. cereus* produces a variety of toxins and is a potential pathogen being able to cause serious infections such as food poisoning, pneumonia, septicaemia, central nervous system infection and endocarditis.[3,4] We report a case of *B. cereus* septicaemia in a 74-year-old immunocompetent male with fatal outcome.

CASE REPORT

A 74-year-old male patient was referred to our university hospital because of fever of unknown origin (FUO). His medical history included a prosthetic mitral valve replacement, a percutaneous transluminal coronary angioplasty with stent placement, both 12 years earlier, and an out-of-hospital cardiac arrest 16 weeks earlier.
The patient had been admitted to the cardiology ward of another hospital three times in the past four months with symptoms of progressive shortness of breath, recurrent fever after discontinuation of antibiotic therapy, night

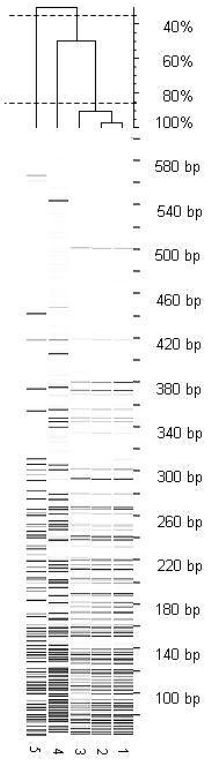
sweats, pancytopenia and eventually septic shock. The patient was treated with vancomycin and gentamicin for suspected endocarditis, and in different courses with clarithromycin, ceftriaxone, ciprofloxacin and co-amoxiclav for a lung infiltrate proven by CT scan. No pathogenic micro-organisms were cultured from sputum or blood. Blood cultures were taken during different hospital admissions and after discontinuation of antibiotics. Despite antibiotic treatment he became septic and was treated with vancomycin and gentamicin. A transoesophageal echocardiography (TEE) revealed no evidence of endocarditis. After one week the patient again developed fever. All antibiotic treatment was stopped and the patient was referred to our hospital because of FUO.

Cultures of blood, urine, sputum, pleural fluid and faeces were negative for pathogenic micro-organisms, including *Mycobacterium tuberculosis*. Polymerase chain reaction on a throat swab and serology for *Mycoplasma pneumoniae* were negative. Serology showed re-activation of Epstein-Barr virus. Tests for hepatitis A, B and C virus, cytomegalovirus, HIV and *Coxiella burnetii* were negative. Pleural fluid was negative for malignant cells, and showed no signs of inflammation (white blood cells $0.6x10^9$/l, lactate dehydrogenase 136 U/l). After eight days without antibiotic treatment a ciprofloxacin-sensitive *Klebsiella pneumoniae* was cultured from sputum. The patient was treated with ciprofloxacin 500 mg twice daily for 16 days. During this treatment his condition improved and his fever disappeared, but the fever returned after termination of the treatment.

Because of a recent stay in Turkey, a bone marrow aspiration was performed to rule out leishmaniasis, brucellosis, mycobacteria and fungi. Culture of the aspirate yielded *Bacillus* sp. which was considered a contaminant. Ten days after the bone marrow aspiration one of six blood culture bottles yielded *Bacillus* sp., also considered a contaminant. However, four days later three out of four additional blood culture bottles yielded *Bacillus* sp. Only now a deep-seated infection with *Bacillus* sp. was suspected. Tested by disk diffusion isolates were susceptible to ciprofloxacin, clindamycin, vancomycin and gentamicin. The patient was treated with vancomycin and ciprofloxacin. A TEE in our hospital revealed no signs of endocarditis. The condition of the patient worsened, with shock and respiratory insufficiency and he was admitted to the intensive care unit for supportive care. He developed multi-organ failure and died despite maximal supportive therapy within 24 hours. No permission for autopsy was given.

The *Bacillus* isolates from bone marrow and blood cultures were identified by matrix-assisted laser desorption and ionisation mass spectrometry time of flight (MALDI-TOF) as *B. cereus*. All blood culture isolates were identical (*figure 1*) by amplified fragment length polymorphism (AFLP).[5]

Figure 1. *Amplified fragment length polymorphism (AFLP) of patient's B. cereus isolates*



Strains with >85% homology are considered identical. 35% homology is the cut-off for isolates considered to belong to the same species. Lane 1-3 patient's blood isolates from three different days; lane 4 B. cereus NCTC 11143; lane 5 TY2666 B. thuringiensis clinical isolate.

DISCUSSION

We describe a case of fatal *B. cereus* septicaemia in an immunocompetent patient. *B. cereus* is a well-known ubiquitous micro-organism and a frequent contaminant of clinical samples.[6] Although *B. cereus* has some pathogenic potency, it is mostly associated with food poisoning due to toxin production.[7] Infrequently, septicaemia, pneumonia, meningitis, and endocarditis are caused by *B. cereus*.[3,4] The majority of these infections occur in immunocompromised patients, intravenous drug users, or newborn babies. However, some patients with *B. cereus* bacteraemia are immunocompetent. Two case reports describe central catheter associated *B. cereus* bacteraemia in an immunocompetent patient.[8,9] Both patients recovered upon catheter removal and antibiotic treatment. Two outbreaks of nosocomial *B. cereus* bacteraemia have been described with 18 and 11 patients, respectively.[10,11] These articles do not clearly mention the immune status of all patients, but it appears that some patients were immunocompetent. Most cases were associated with central catheters and some even with contaminated intravenous fluid.[11]

We concluded that our elderly patient was immunocompetent, because he had no history of recurrent infections, nor was he taking immunosuppressive medication. Recent CT scans did not show signs of malignancy and an extensive panel of autoimmune markers was negative. In addition to this, the pathology report on his bone marrow was in agreement with ongoing *B. cereus* septicaemia. *B. cereus* was late to be recognised as a causative pathogen due to several factors. First, all blood cultures collected during the first three admissions in the other hospital remained negative. Also no *Bacillus* species were reported as contaminants. The first positive blood culture in our hospital yielded *B. cereus* in only one out of six bottles. Due to these factors, adequate treatment was stopped after a short period. Our patient had a mechanical mitral valve, which made him more susceptible to endocarditis. According to the Duke criteria, the diagnosis was possible infective endocarditis.[12] Despite the fact that with repeated TEEs no definite diagnosis could be made, endocarditis is still the most probable diagnosis. A nosocomial infection introduced in our hospital can not be ruled out because blood cultures in the other hospital yielded no micro-organisms.

B. cereus endocarditis is associated with prosthetic valves or pacemaker leads.[13] With the increasing age of patients, more and more patients will have artificial cardiac valves. These patients are probably more susceptible to deep-seated infections with micro-organisms of low virulence. In immunocompetent patients with artificial material, positive blood cultures with *Bacillus* species should be carefully evaluated even when the TEE does not show signs of an endocarditis. When a response on antimicrobial treatment is observed, longer treatment duration must be considered.

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SPECIAL ARTICLE

Nurse practitioners improve quality of care in chronic kidney disease: two-year results of a randomised study

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ABSTRACT

Background: Chronic kidney disease (CKD) is associated with increased cardiovascular risk. Here we evaluate whether strict implementation of guidelines aimed at multiple targets with the aid of nurse practitioners (NP) improves management in patients with CKD.

Methods: MASTERPLAN is a randomised controlled clinical trial, performed in nine Dutch hospitals. Patients with CKD (estimated glomerular filtration rate (eGFR) 20-70 ml/min) were randomised to receive NP support (intervention group (IG)) or physician care (control group (CG)). Patients were followed for a median of five years. Presented data are an interim analysis on risk factor control at two-year follow-up.

Results: We included 788 patients (532 M, 256 F), (393 CG, 395 IG), mean (±SD) age 59 (±13) years, eGFR 38 (±15) ml/min/1.73m2, blood pressure (BP) 138 (±21)/80 (±11) mmHg. At two years 698 patients (352 IG, 346 CG) could be analysed. IG as compared with CG had lower systolic (133 *vs* 135 mmHg; p= 0.04) and diastolic BP (77 *vs* 80 mmHg; p=0.007), LDL cholesterol (2.30 *vs* 2.45 mmol/l; p= 0.03), and increased use of ACE inhibitors, statins, aspirin and vitamin D. The intervention had no effect on smoking cessation, body weight, physical activity or sodium excretion.

Conclusion: In both groups, risk factor management improved. However, changes in BP control, lipid management and medication use were more pronounced in IG than in CG. Lifestyle interventions were not effective. Coaching by NPs thus benefits everyday care of CKD patients. Whether these changes translate into improvement in clinical endpoints remains to be established.

KEYWORDS

Blood pressure, cardiovascular disease, clinical epidemiology, chronic kidney disease, dyslipidaemia

INTRODUCTION

Chronic kidney disease (CKD) is consistently related to excess cardiovascular morbidity and mortality. The benefits of blood pressure (BP) management on cardiovascular risk in CKD have not been shown in dedicated trials although several post-hoc subgroup analyses among CKD patients have suggested benefit.[1,2] Only recently, statins were shown to be effective to reduce cardiovascular risk in CKD patients in the Study of Heart and Renal Protection.[3] Up till now intervention studies targeting other single risk factors to lower cardiovascular events (ADVANCE, CREATE, CHOIR) have not been very successful in CKD patients.[4-6]

Similarly, few strategies besides lowering of BP and proteinuria have proven effective to attenuate the deterioration of renal function in patients with CKD.[7]

One of the possible explanations is that CKD is a multifactorial disease process in which both traditional cardiovascular risk factors and non-traditional risk factors (inflammation, CKD-metabolic bone disease, anaemia, proteinuria) interact. No single factor may play the major causative role. Based on this hypothesis it can be expected that a multifactorial approach is the most appropriate way to reduce cardiovascular morbidity and preserve kidney function in patients with CKD. Such a strategy was proven effective in diabetic patients.[8]

Indeed, guidelines for the treatment of CKD involve management directed at multiple treatment targets. The guidelines published in 2003-2005, however, were based upon extrapolation from other populations because of the paucity of data in patients with CKD.[9] Implementation of these guidelines in routine clinical practice is difficult. We, and others, have shown that treatment targets are often not met.[10-12] In addition, differences between centres were present.[13,14] Positive results from single-centre studies may therefore not be generalisable.

To address the need for improvement in CKD care we evaluated the added value of specifically trained nurses in the care of CKD patients. In similar study protocols, specialised nurses, cooperating in teams with doctors, have improved care in outpatients with diabetes, myocardial infarction and heart failure.[8,15-17]

To evaluate this hypothesis the randomised controlled Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners (MASTERPLAN) study was designed. We present the interim results after two years of follow-up on improvement in care, attainment of treatment targets, and between-centre differences. The primary endpoints will be reported when available in another paper, expected 2012.

MATERIALS AND METHODS

The MASTERPLAN study [Trial registration ISRCTN registry: 73187232 (http://isrctn.org)] is a randomised controlled trial conducted in nine hospitals with a nephrology department in the Netherlands. The trial is reported in accordance with the CONSORT guidelines.[18]

Rationale and design have been published elsewhere.[19,20] The effects of a multitargeted treatment regimen executed by a specialised nurse under the supervision of, and in collaboration with, a nephrologist are compared with the care delivered by the patients own nephrologists. In both arms of the study, the same treatment guidelines apply. The primary endpoint is a composite nonfatal myocardial infarction, stroke and cardiovascular mortality. Secondary endpoints are all-cause mortality, achievement of treatment goals for the various risk factors, decline of kidney function and quality of life.

Patients were eligible for inclusion when 18 years or older and diagnosed with CKD with a creatinine clearance estimated by the Cockcroft-Gault equation between 20 and 70 ml/min. The following conditions were considered exclusion criteria:

- A kidney transplant less than a year before inclusion.
- Acute kidney failure or rapidly progressive glomerulonephritis established by the treating physician.
- Any malignancy less than five years before inclusion other than basocellular or squamous cell carcinoma of the skin.
- Participation in other clinical trials requiring the use of study medication.

Recruitment began in April 2004 and continued until December 2005. From April 15th 2005 until the end of the inclusion period the Cockcroft-Gault equation was modified to take into account body surface area according to then prevailing insights into the applicability of formulas to estimate renal function.[21-24] This modification was approved by the medical ethics committee.

After the baseline evaluation, the patients were randomised to either nurse practitioner (NP) care or usual care in a 1:1 ratio. Randomisation to treatment was stratified by centre, gender and kidney transplant status using a web-based randomisation module and performed in predefined blocks. Patient, NP and physician were familiar with the treatment allocation. All investigators handling the data, however, were blinded until June 2010. Follow-up continued until June 2010. Endpoint evaluation and data analysis is scheduled for end 2011/beginning 2012. The study was approved by an institutional medical ethics committee and all subjects gave informed consent.

All participating hospitals were teaching hospitals that offered a full range of nephrology treatment including kidney replacement therapy (both haemodialysis and peritoneal dialysis) and were involved in the care of kidney transplant recipients. Three hospitals were university clinics that offered tertiary care and had kidney transplant programs. The number of beds per hospital ranged from 414 to 953.

The same set of guidelines and treatment goals applied to all patients. Both patients and physicians were provided with information about the beneficial effects of multifactorial risk factor management regardless of treatment allocation. In the intervention group NPs, supervised by a qualified nephrologist, actively pursued lifestyle intervention (physical activity, nutritional counselling, weight reduction and smoking cessation), the use of specified cardioprotective medication and the implementation of current guidelines. The NP regularly checked whether treatment goals were met

and when deemed appropriate adjusted treatment to achieve target values. Modification of therapy was executed according to flowcharts that were derived from then current guidelines. For lifestyle-modifiable risk factors the NP applied motivational interviewing as a technique to improve lifestyle in the intervention group.[11] In the intervention group patients were also seen by their nephrologist regularly (although no minimum frequency was required in the study protocol). Acetylsalicylic acid was included in the intervention because of the then proposed status of CKD as a coronary heart disease risk equivalent and the possible (but untested) benefits of acetylsalicylic acid in this context.[25,26] This was in line with a then valid guideline firmly advocating the use of aspirin in primary prevention in patients with diabetes mellitus (which was, however, downgraded in a later version).[27,28] Use of aspirin as primary prevention was deemed contraindicated by protocol if patients had a history of a cerebral haemorrhagic event, autosomal dominant polycystic disease with a family history of cerebral haemorrhagic events, a known bleeding tendency or a history of pyrosis, reflux or gastrointestinal bleeding.

Physician care comprised 'usual care'. In contrast to the intervention group and in agreement with real-life practice no extra incentives to adhere to the guidelines were supplied.

Patients in the intervention group visited the NP at least every three months, whereas the frequency of visits of the control patients was left to the discretion of their nephrologist. Medication use was recorded every three months in an online case report form as were office BP, bodyweight and predefined laboratory measurements. In both patient groups twice yearly standardised oscillometric BP measurements after 15 minutes of supine rest were taken. Ankle brachial index and evaluation of endpoints were performed annually in both intervention and control groups. Additionally patients filled out questionnaires regarding quality of life and physical activity on a yearly basis. Under the assumption that patients were in a steady state, sodium excretion was applied as a measure of sodium intake. Blood was drawn and a 24-hour urine sample was collected. Blood and urine samples were analysed locally. Medical history was obtained from the medical records. History of CV disease was defined as a history of myocardial infarction, stroke or vascular intervention. Diabetes mellitus (DM) at baseline was defined as the use of glucose-lowering drugs or a fasting glucose over 7.0 mmol/l. Adherence to the Dutch Guidelines of Healthy Physical exercise was determined with the validated SQUASH questionnaire.[29] The underlying diagnosis of kidney disease was determined by the treating physician and categorised using the ERA-EDTA (European Renal Association) registration criteria. To allow for comparisons with other studies, we report eGFR using the abbreviated MDRD formula.[30]

STATISTICAL ANALYSIS

Baseline characteristics are expressed as means (SD) or proportions. For non-parametric data medians [range] have been supplied.

To address the effect of the intervention on risk factors after two years of follow-up we used generalised estimating equations (GEE) to assess time-dependent mean changes in risk factors within and between treatment arms.

The main assumption of the GEE approach is that measurements are assumed to be dependent within subjects and independent between subjects. The correlation matrix that represented the within-subject dependencies was estimated using an autoregressive relationship (i.e., correlation between variables within subjects are assumed to decline with time between the measurements). For the current analysis, the interest was in the mean difference over time in risk factor levels between treatment arms. GEE analyses were performed using the on-trial measurements with adjustments for baseline measurements. All p values were two-sided, and p values less than 0.05 were considered to indicate statistical significance. No adjustment for multiple statistical testing was made.[31]

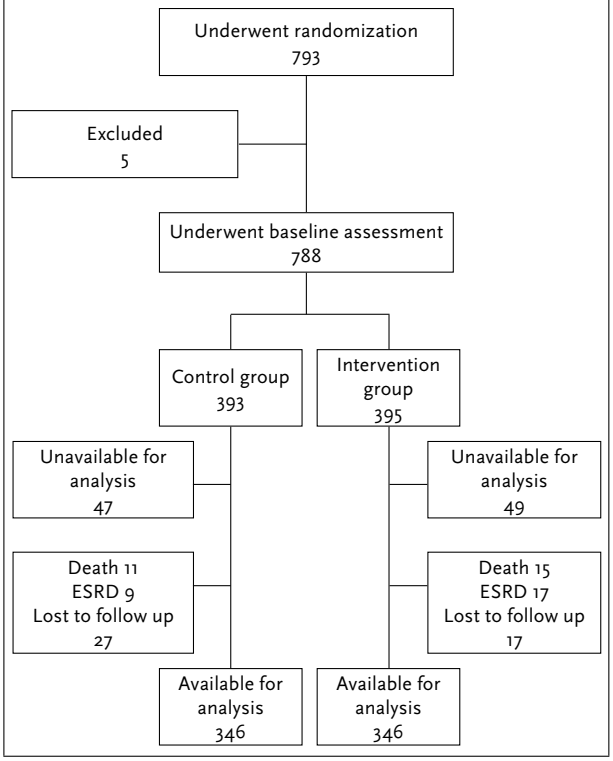
We also evaluated if the specialised nursing care reduced the differences in care between centres. To this end we calculated the absolute difference between the group mean and centre mean for each risk factor. Relation of the absolute differences between group means and centre means with time was then calculated using a Spearman correlation coefficient, with a negative correlation illustrating a reduction of between-centre differences over time. All analyses were performed with SPSS 17.0 (SPSS inc., Chicago, USA).

RESULTS

About 60% of patients deemed eligible by their physician and asked to participate in the study actually participated and were included. The main reasons for non-participation were reluctance of the patient to changes in drug therapy and inability of the patient to attend the required visits.

A total of 793 patients were included in the study. Three patients did not meet inclusion criteria and two declined participation after randomisation. At two years of follow-up 346 patients in the control group and 352 patients in the intervention group were available for analysis (*figure 1*). Baseline demographics are shown in *table 1*. The mean age of patients was 59 (±13) years; 6.7% of patients are KDOQI CKD class 1 or 2, 60.8% class 3, 30.2% class 4 and 2.4% class 5. Of the patients, 17% had no albuminuria, 49% had microalbuminuria and 34% had overt proteinuria. All characteristics were well balanced between the groups

Figure 1. *Enrolment, randomization, and follow-up of study participants*



apart from a history of cardiovascular disease which was more prevalent in the intervention group and current smoking which was less prevalent in the intervention group.

The changes in risk factors after one and two years are shown in *table 2*. In both the intervention and control group changes in several risk factors were found. In both groups the systolic BP, diastolic BP, LDL cholesterol, haemoglobin and percentage of smokers decreased. In both groups statistically significant reductions in eGFR and an increase in use of ACE inhibitors or angiotensin receptor blockers, statins, vitamin D and aspirin were found (*table 2*).

Systolic BP, diastolic BP and LDL cholesterol were lower in the intervention group at two years and also declined significantly more than in the control group. At two years the difference between the two groups was 2 mmHg for systolic, 3 mmHg for diastolic BP and 0.15 mmol/l for LDL cholesterol. Use of cardioprotective medication increased more after two years in the intervention group than in the control group: ACE inhibitors or angiotensin receptor blockers (+8.6% *vs* +3.7%), statins (+21.2% *vs* 14.2%), acetylsalicylic acid (+23.4% *vs* +9.4%) and vitamin D supplements (+28.4% *vs* 16.1%). Of the patients in the intervention group, 20.4% used coumarin derivatives and an additional 4.3% had a contraindication and were therefore not prescribed acetylsalicylic acid.

Table 1. *Baseline characteristics*

Parameter	Control group (n=393)	Intervention group (n=395)
Age (years)	59.3 (12.8)	58.9 (13.1)
Gender (male) (%)	68	67
Race (Caucasian)	93	91
Nephrological diagnosis (%)		
Diabetic nephropathy	9	11
Renovascular	28	26
Glomerulonephritis/ interstitial nephritis	34	28
Congenital disease	13	11
Unknown	16	24
Kidney transplantation (%)	14	14
Prior CV disease by questionnaire (%)	25	33
Creatinine (mcmol/l)	181 (67)	182 (64)
eGFR (ml/min/1.73m2)	37.7 (14.0)	38.4 (15.2)
Office systolic BP (mmHg)	139 (22)	138 (20)
Office diastolic BP (mmHg)	81 (11)	80 (11)
Proteinuria (g/24 h) Median [25th/75th percentile]	0.3 [0.1-0.8]	0.2 [0.1-0.8]
Albumin creatinine ratio (mg/mmol) Median [25th/75th percentile]	18.8 [6.8-51.9]	15.0 [5.6-47.5]
LDL cholesterol (mmol/l)	2.74 (0.90)	2.78 (0.95)
Haemoglobin (mmol/l)	8.2 (1.0)	8.2 (1.0)
History of DM (%)a	23	26
Phosphate (mmol/l)	1.10 (0.24)	1.10 (0.25)
PTH (pmol/l) [median 25th/75th percentile]	9 [5-14]	9 [5-15]
Sodium excretion (mmol/24 h) [median 25th/75th percentile]	150 [113-189]	148 [116-195]
BMI (kg/m2)	27.2 (4.9)	27.0 (4.6)
Physical exercise (adherence to Dutch physical activity guideline) (%)	60	57
Physical activity (activity score=intensity/min/week/1000)	6182 (4467)	5803 (3891)
Smoking (%)	24	19

Values are proportions, means with corresponding standard deviation, or median with inter-quartile ranges, whenever appropriate. a: History of diabetes mellitus defined as using blood glucose lowering medication or fasting glucose >7.0 mmol/l. CV = cardiovascular; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; DM = diabetes mellitus, PTH = parathyroid hormone; BMI = body mass index.

In contrast, there were no significant changes in lifestyle variables between the groups.

At two years 46% of patients achieved the BP goal in the intervention group whereas this was only 35% in the control group (p=0.003). For the LDL goal this was 69% and 60% respectively (p=0.02).

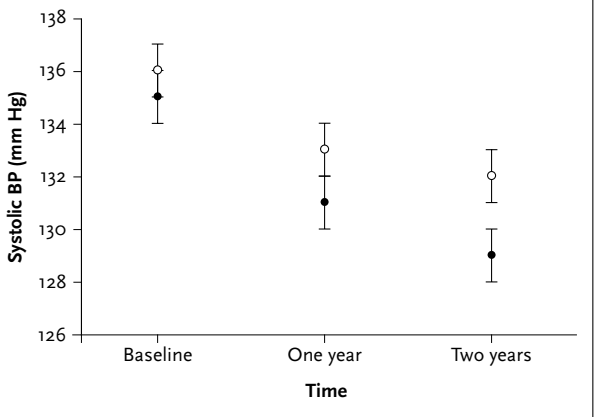
Table 2 and *figure 2* illustrate that the effect of most interventions was most prominent in the first year of the study. Changes were maintained during the second year. This applies both for the intervention and the control group.

Table 2. *Effects of the intervention after one and two years*

Parameter	Baseline		Year 1		Year 2		p-value for differences between treatment group
	Control	Intervention	Control	Intervention	Control	Intervention	
N	393	395	373	374	346	352	
eGFR (ml/min/1.73m²)	37.7 (14.0)	38.4 (15.2)	35.8 (15.2)	36.7 (15.6)	35.0 (16.2)*	36.2 (16.4)*	0.36
Office systolic BP (mmHg)	139 (22)	138 (20)	137 (20)	133 (20)	135 (19)*	133 (21)*	0.04
Office diastolic BP (mmHg)	81 (11)	80 (11)	80 (11)	78 (11)	80 (11)*	77 (10)*	0.007
Proteinuria (g/24 h)	0.3 [0.1-0.8]	0.2 [0.1-0.8]	0.3 [0.1-1.0]	0.2 [0.1-0.8]	0.3 [0.1-1.0]	0.2 [0.1-0.7]	0.33
Albumin-creatinine ratio (mg/mmol)	18.8 [6.8-51.9]	15.0 [5.6-47.5]	17.7 [6.6-53.1]	13.4 [4.7-41.1]	19.1 [7.0-62.4]	12.3 [5.0-46.3]	0.56
LDL cholesterol (mmol/l)	2.74 (0.90)	2.78 (0.95)	2.53 (0.89)	2.33 (0.74)	2.45 (0.81)*	2.30 (0.75)*	0.03
Haemoglobin (mmol/l)	8.2 (1.0)	8.2 (1.0)	8.1 (1.0)	8.1 (1.0)	8.0 (1.1)*	8.1 (1.1)	0.85
HbA1C (%)	6.1 (0.9)	6.1 (0.9)	6.1 (0.9)	6.1 (0.8)	6.1 (0.9)	6.1 (0.8)	0.95
Phosphate (mmol/l)	1.1 (0.2)	1.1 (0.2)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	0.70
Calcium (mmol/l)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	0.43
PTH (pmol/l)	9 [5-14]	9 [5-15]	8 [5-14]	8 [5-14]	9 [6-15]	9 [5-15]	0.64
Sodium excretion (mmol/24 h)	150 [113-189]	148 [116-195]	152 [120-191]	149 [116-198]	150 [117-190]	150 [120-193]	0.95
BMI (kg/m²)	27.2 (4.9)	27.0 (4.6)	27.1 (4.9)	26.8 (4.6)	27.0 (4.7)	26.8 (4.7)	0.53
Physical activity (intensity/min/week/1000)	5220 [3180-8520]	5175 [2885-7930]	4740 [2689-7380]	4800 [2100-7740]	5340 [2465-7793]	4920 [2330-7628]	0.31
Smoking (%)	24	19	22	16	17*	14	0.06
Use of ACE or ARB (%)	77.6	81.1	84.0	91.6	81.3*	89.7*	0.003
Use of statin (%)	63.4	66.9	74.8	87.7	77.6*	88.1*	<0.001
Use of acetyl salicylic acid (%)	34.6	39.4	46.2	63.4	44.0*	62.8*	<0.001
Use of vitamin D (%)	23.9	22.0	32.8	40.9	40.0*	50.4*	0.05
Use of phosphate binder (%)	13.2	9.6	15.2	11.0	18.4*	15.3	0.11

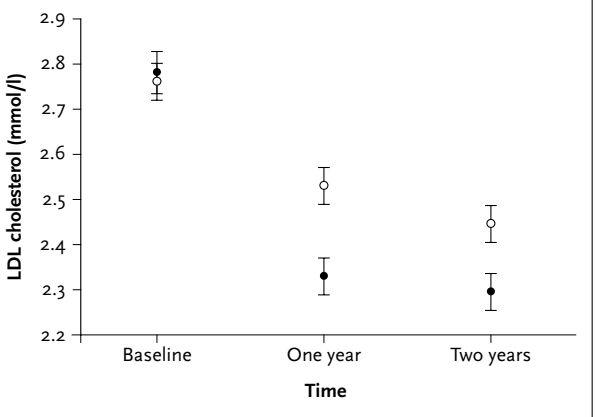
eGFR = estimated glomerular filtration rate; BP = blood pressure; LDL = low-density lipoprotein; PTH = parathyroid hormone; BMI = body mass index; ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; * = p-value for change over time within treatment group <0.05, results are mean (± sd) or median [25th-75th percentile].

Figure 2A. *Changes in systolic BP in the first two years of the study*



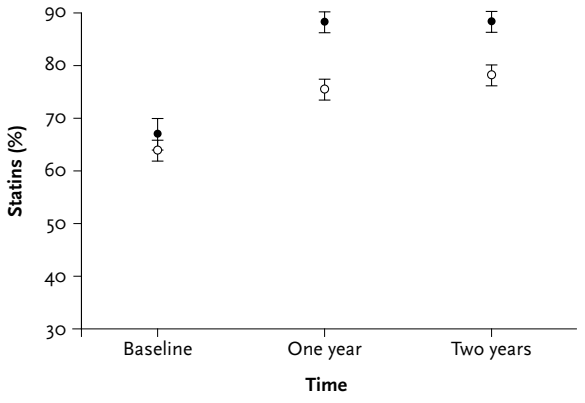
● = Intervention group (p value for change within group <0.001); o = control group (p value for change within group 0.004); p value for change between groups 0.04.

Figure 2B. *Changes in LDL cholesterol in the first two years of the study*



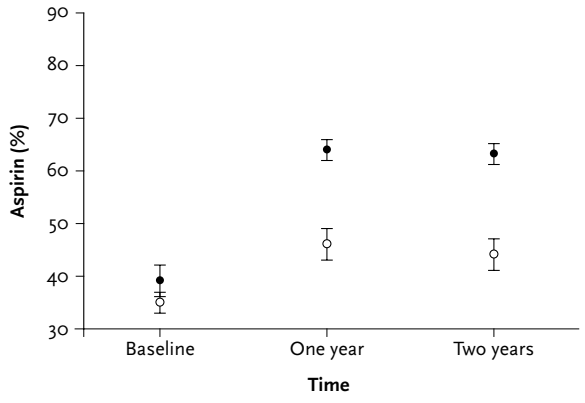
● = Intervention group (p value for change within group <0.001); o = control group (p value for change within group <0.001); p value for change between groups 0.03.

Figure 2C. *Changes in statin use in the first two years of the study*



● = Intervention group (p value for change within group <0.001); o = control group (p value for change within group <0.001); p value for change between groups <0.001.

Figure 2D. *Changes in aspirin use in the first two years of the study*



● = Intervention group (p value for change within group <0.001); o = control group (p value for change within group 0.008); p value for change between groups <0.001.

Table 3 shows the number of visits performed in the first two years of the study. There were more visits in the intervention arm but significantly less visits to the specialist.

We previously showed that differences in quality of care and BP between centres could be partially attributed to physician-related factors.[13] Therefore we hypothesised that the execution of patient care by uniformly trained NPs would attenuate between-centre differences. This was analysed by comparing the centre means for the variables influenced by the intervention (systolic BP and LDL cholesterol) to the cohort mean at baseline, one year and two years. For both risk factors the variation between the centres decreased with time in the intervention group as illustrated in *figure 3*.

DISCUSSION

Our study showed that added support by highly qualified NPs improved the quality of treatment of patients with CKD. Specifically, we observed lower blood pressures, lower LDL cholesterol, and increased use of aspirin, vitamin D, and ACE inhibitors in the intervention group. However, in contrast with our expectations, the NP-guided intervention did not result in major changes in lifestyle factors.

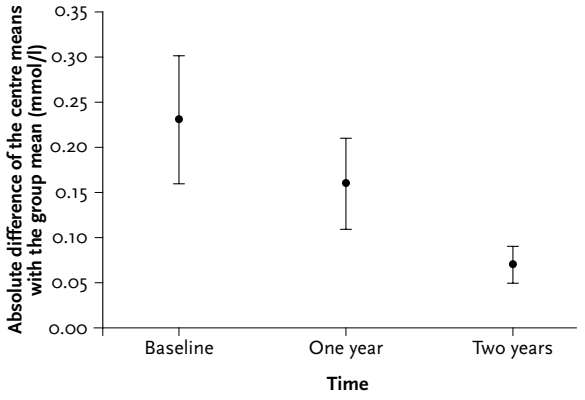
Many studies have evaluated the effect of NP support in attaining treatment targets. Most studies were conducted in patients with diabetes[8,32-35] or patients with a high cardiovascular risk score.[36-40] They showed improvement in the management of some risk factors compared with usual care. In general, pharmacotherapy modifiable risk factors such as BP and cholesterol improved in the intervention groups, although in many studies beneficial effects were limited to only one of the evaluated interventions.[8,33,35,37,40,41] The size of the improvements of risk factors between baseline and two years in the intervention group particularly with regard to BP and LDL might well represent relevant improvements in cardiovascular risk.[42,43] However, whether the smaller difference between intervention and control group in this study translates to improved cardiovascular risk after longer follow-up still remains to be established. Some argue that multiple moderate improvements in several areas of risk factor

Table 3. *Number of visits per year in the first two years of the study in the control and intervention group*

	Control			Intervention		
Year	Total visits	NP visits	Physician visits	Total visits	NP visits	Physician visits
1	4.6 (2.3)	1.0 (0.3)	3.6 (2.3)	7.4 (2.2)#	4.7 (1.4)	2.7 (1.9)*
2	4.7 (2.9)	1.0 (0.4)	3.7 (2.9)	7.0 (2.7)#	4.2 (1.4)	2.8 (2.2)*

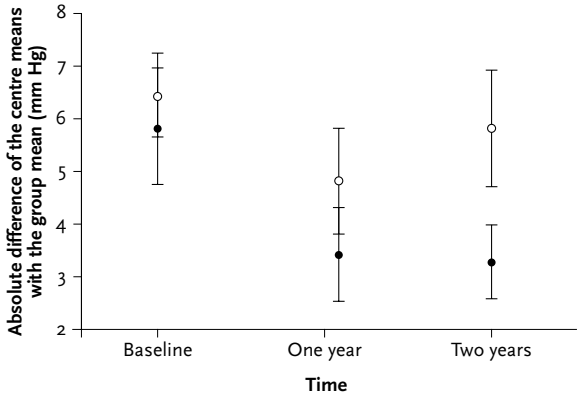
 # p value for difference between intervention and control for total visits <0.001; *p value for difference between intervention and control for physician visits <0.001. NP = nurse practitioner.

Figure 3A. *Centre differences for LDL cholesterol*



● = Intervention group (p value for change within group 0.003).

Figure 3B. *Centre differences for systolic BP*



● = Intervention group (p value for change within group 0.04).

management may translate into larger benefits on hard endpoints, as was also shown in the study by Gaede *et al.*[8,44,45]

It is unclear whether even lower BP goals would have resulted in lower BP in the intervention group. A recent study in 500 Canadian patients with stage 3-4 CKD followed for two years compared family physician care with care by a specialised nurse under supervision of a nephrologist. They failed to observe beneficial changes in BP and lipid profile and also did not note any difference on cardiovascular endpoints.[46] The patients in the CanPREVENT study were older, had better kidney function (higher eGFR and lower proteinuria) and had better controlled systolic BP (on average 8 mmHg lower) at baseline. These differences can certainly explain the different results between CanPREVENT and MASTERPLAN.

We hypothesised that specialised nursing care could also be of particular benefit by helping patients to improve their lifestyle. In our current analysis no such effect was observed. This was also reported by Gaede *et al.* They studied patients with diabetes mellitus type 2 and observed improvement in BP, cholesterol, glycaemic control and aspirin use. In contrast, lifestyle factors were not affected.[8,47] Earlier NP-led single intervention studies did show benefit in modifying the lifestyle factors studied in our study (smoking cessation, weight loss , dietary sodium restriction and physical activity).[48-53] In contrast, many recent reports in preventive medicine have pointed out the difficulties in reaching any relevant benefits in studies investigating a multiple health behavioural change. Effects were, if any, mostly limited in size.[39,54,55] A recent review by Blokstra *et al.* in patients with established cardiovascular disease concluded that a multifactorial lifestyle intervention can affect diet, activity, smoking behaviour and reduce the occurrence of cardiovascular disease and/or mortality particularly in high-risk groups.[56] The original studies described had a far more rigorous lifestyle intervention than was applied in our study.[57] In other high-risk categories the results were far less outspoken, possibly suggesting that patients who had experienced a cardiovascular event were more motivated to execute lifestyle changes.[56]

Why then were no lifestyle benefits found in our cohort? Firstly CKD is a silent disease, and all efforts are taken as preventive measures. It is likely that CKD patients have lower motivation to ameliorate lifestyle than patients who have experienced a cardiovascular event. Secondly Jacobs *et al.* suggested that in a multifactorial intervention the number of possible choices may overwhelm the participants and thus result in lower effects.[58] This might also be relevant in our study, since we have formulated 11 treatment targets for our patients, four of which are to be considered lifestyle interventions.

Finally another effect might be relevant not only with regard to lifestyle but also with regard to other risk factors. Because of the study design, patients were randomised within a centre; therefore the same physician coaching the NP would see patients of the control group during their outpatient visits. Patients in the control group might thus also experience better care than they would have received had they been treated in a centre not associated with the study. A possible indication of this is the clear reduction in the percentage of smokers in both cohorts. This effect is further illustrated in the control group by the reduction of LDL cholesterol and the rapid increase in the prescription of statins and aspirin during the first year of the study (*figure 2*). The increase in treatment of cardiovascular risk factors in the control group could also be explained in another fashion, namely as a consequence

of an increased nationwide awareness of cardiovascular risk in this decennium. Several key publications and guidelines were published prior to or during the early years of our study and may have prompted physicians to alter their therapeutic strategy (e.g. KDOQi and Dutch federation of Nephrology guidelines).[59,60]

Patients were seen more frequently in the intervention group (*table 3*). This was part of the study design and could be a factor in the observed difference in BP and LDL cholesterol; however, apparently this did not affect changes in lifestyle.

Earlier we reported clear between-centre differences for several risk factors and explored this phenomenon more thoroughly for blood pressure.[13,14] We suggested that physician-related factors might explain some of the differences. Our current data support this view, since between-centre differences were less for those risk factors that were improved in the nursing intervention group.

We conclude that specialised nursing care can help to improve specialist nephrological care to patients with stage 3 and 4 CKD. This is readily apparent with pharmacotherapy modifiable risk factors, but less so with lifestyle interventions. Whether this translates into improved cardiovascular risk remains to be established during the remainder of the follow-up of the study.

LIMITATIONS OF THE ANALYSIS

Not all interventions applied in our study can be considered evidence based or part of the then current guidelines. Patients with an eGFR below 50 ml/min/1.73 m2 were supposed to receive active vitamin D and certainly more current guidelines suggest measurement of vitamin D before supplementation.[61] Also aspirin was advocated in our study based upon the conviction of the study group that this might be beneficial in CKD, just like other groups had suggested.[25,26,62]

Another limitation is the earlier mentioned evident improvement of risk factor management in the control group. The effect of improved care in the control group could be an explanation for the modest differences between intervention and control and might also influence the effect on cardiovascular events.

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These data were presented at:

- Highlights in Nephrology, Papendal: Nurse practitioner care voor patiënten met CKD: resultaten van de MASTERPLAN-studie. December 2010.
- The Dutch Nephrology Congress, Veldhoven: Effect of a multifactorial intervention with the aid of nurse practitioners in patients with chronic kidney disease: two years results from a randomised controlled trial. March 2011.
- EDTA, Prague: Effect of a multifactorial intervention with the aid of nurse practitioners in patients with chronic kidney disease: two years results from a randomised controlled trial. Juni 2011.

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Netherlands
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PHOTO QUIZ

Exudative retinal detachment

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On 6 February 2010, a 50-year-old female patient was admitted to a local hospital complaining of sudden dropping of the left eye's visual acuity. B-scan ultrasonogram showed retinal detachment but failed to demonstrate a solid subretinal mass. A few days later, the same patient complained of hoarseness of her voice. On 6 March 2010, the otolaryngologist found paralysis of the left vocal cord, through the laryngoscope. The patient was referred to our hospital for the blurred vision of the left eye and hoarseness of her voice. Her visual acuity was 20/20 in the right eye and HM/5 cm in the left eye. Ophthalmoscope revealed exudative retinal detachment (*figure 1*). Contrast-enhanced CT scan confirmed an enhanced lesion on the temporal side of the left eyeball with a dense central area. Ultasonography showed a mass of about 21x8 mm, 7 mm thick, without acoustic shadowing or gradual decay (*figure 2*). Meanwhile, the ribbon-shaped hyper-zone between the papilla optica and para-lens were seen. On 9 April 2010, the patient developed a lung infection; computed tomography (CT) of the chest demonstrated a mass in the hilum of left lung (*figure 3*). The biopsy was performed and the histopathology examination confirmed that the mass was small lung cell carcinoma.

Figure 1. *The exudative retinal detachment on the temporal side of left eyeball without retinal tears*

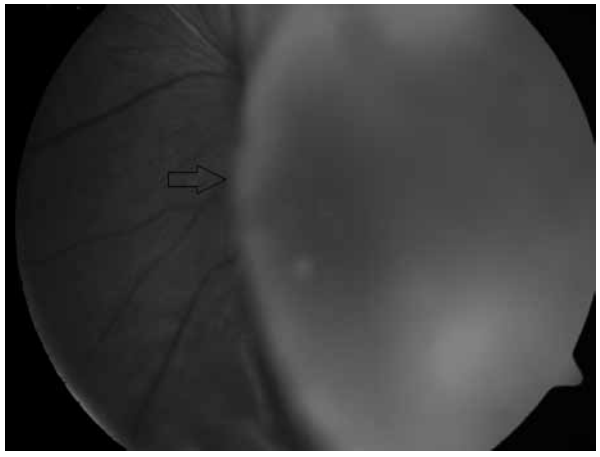

Figure 2. *Sonogram of the lesion with hyperecho ribbon-shaped*

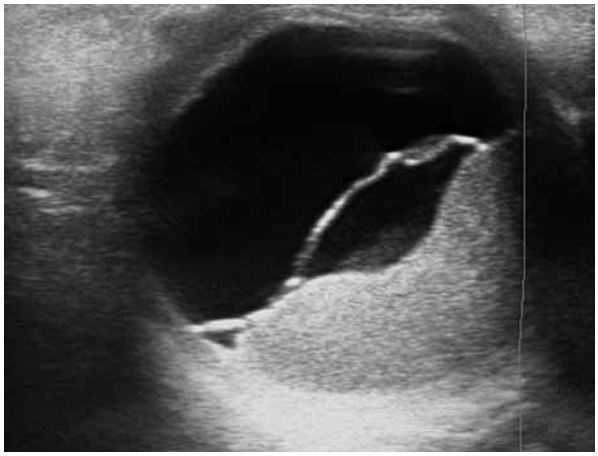

Figure 3. *Enhanced chest computed tomography revealed a large mass in the hilum of the left lung. The mass was diagnosed as small cell lung cancer by bronchoscopic biopsy*

WHAT IS YOUR DIAGNOSIS?

See page 530 for the answer to this photo quiz.w

PHOTO QUIZ

Failing hormones

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CASE REPORT

A 70-year-old female patient presented to the outpatient clinic with general malaise, salt craving, and hypotension. She had been treated for severe asthma with 15 mg prednisone daily without interruptions for at least ten years. This treatment was complicated by the development of diabetes mellitus and severe osteoporosis. In addition, she suffered from generalised myopathy and skeletal pain, for which she took naproxen 500 mg three times a day.

On clinical examination, a wheel-chair dependent, 71-year-old woman was seen with a moon face, buffalo hump, abdominal fat accumulation, and severe muscle atrophy (*figure 1*). Her blood pressure, however, was low (110/60), both in supine and in upright position.

Sodium concentration was 126 mmol/l, potassium 4.9 mmol/l, creatinine 59 umol/l and plasma osmolality 244 mOsm/kg. Urinary sodium concentration was 43 mmol/l. ACTH was suppressed (<5 ng/l), with a normal afternoon cortisol level (0.293 µg/l). Plasma renin activity was undetectable (<0.10 µg/l/hour), and aldosterone concentration was low (0.13 nmol/l, reference range 0.0 to 0.35 nmol/l). The transtubular potassium gradient (TTPG = (Urine potassium/ (urine osmol/serum osmol))/ serum potassium)) was 3.7 (reference >7)

WHAT IS YOUR DIAGNOSIS?

See page 532 for the answer to this photo quiz.

Figure 1.

A. Moon face
B. Buffalo hump
C. Muscle atrophy of the right hand

Netherlands
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Marked bradycardia in a young woman with weight loss

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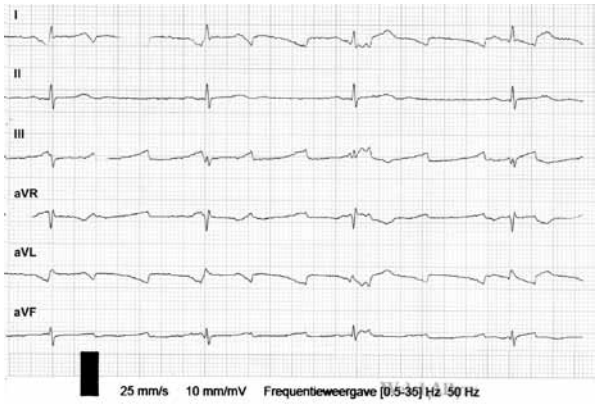
CASE REPORT

A 21-year-old woman with a history of disabling irritable bowel syndrome (IBS) was admitted to the internal medicine ward with abdominal pain. During the last few weeks she had experienced a 15% weight loss due to malnourishment secondary to the abdominal complaints and light-headedness upon standing, but no syncope. Because of a regular heart rate of 35 beats/min an electrocardiogram was taken (*figure 1*) after which she was transferred to the cardiology department for further examination and observation. All laboratory analyses including serum sodium, potassium, magnesium, calcium, phosphate and thyroid-stimulating hormone were in the normal range. The medication used by our patient was not known to influence cardiac conduction or cause arrhythmias.

Figure 1. *Electrocardiogram with a bradycardia*



WHAT IS YOUR DIAGNOSIS?

See page 533 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 527)

EXUDATIVE RETINAL DETACHMENT

DIAGNOSIS

Symptomatic choroidal metastases from lung cancer are only found in a minority of patients.[1] Visual loss with retinal detachment is a rare clinical complication of small cell lung cancer.[2-4] To our best knowledge, this patient is unique in that she had choroidal metastases and exudative retinal detachment as the presenting sign of small cell carcinoma of the lung. The lesion radiologically mimics choroidal melanoma complicated with retinal detachment. The diagnosis is confirmed by bronchoscopic biopsy of the mass, which is shown to be small lung cell carcinoma through histopathology examination. The patient responded to systemic chemotherapy and radioactive plaque therapy. It should not be ignored that choroidal solitary mass might also originate from the lung. The aetiology and nature of the lesion should be well investigated, in particular when the vision loses expeditiously within a short period.

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PHOTO QUIZ

A hairy problem

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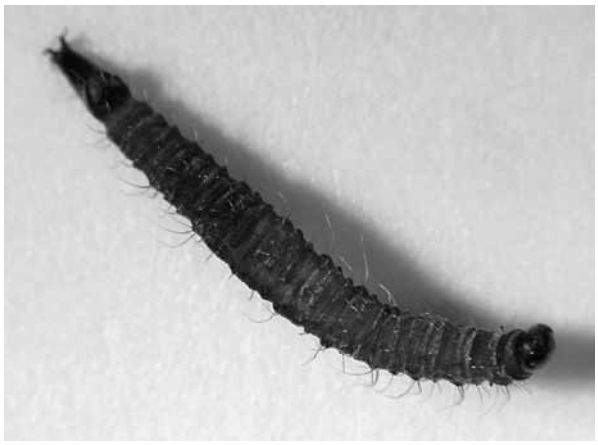
CASE REPORT

An 18-year-old woman presented to our outpatient clinic three days after her return from Playa del Carmen, near Cancun, Mexico, where she had spent her 14-day holiday in a luxury beach resort. She did not have any sexual encounters during her stay. On the last day of her visit, during the first days of her menses, she had anxiously observed small moving objects in her menses secretions in the bath tub sink after washing herself in the hotel bathroom. To ensure the moving, living objects were not residing in the bath, she had cleaned the bath and washed herself again. Once more she observed one or two small black curling and twitching creatures. In the days prior to these observations she had not experienced any itching, local skin abnormalities or vaginal discharge. Notably, she had caught one organism from the bath and stored it in a contact lens container. After her return to the Netherlands she visited her general practitioner, who, after a non-revelatory internal medical examination, referred her to the our travel clinic. Upon physical examination the patient did not show any abnormalities. Visualisation of the deceased organism under a dissection microscope revealed a blackish wormlike insect larva with multiple body segments and rings, protruding hairs and clearly defined head and tail, 6 mm in length and 0.5 mm in width (*figure 1*).

Figure 1. Larva of Clogmia albipunctata as retained by our traveller (length approx. 6 mm)



WHAT IS YOUR DIAGNOSIS?

See page 534 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 528)

FAILING HORMONES

DIAGNOSIS

The clinical signs, symptoms and laboratory investigations point towards symptomatic hyporeninaemic hypoaldosteronism in the presence of exogenous Cushing's syndrome.

The syndrome of hyporeninaemic hypoaldosteronism is characterised by decreased angiotensin II production secondary to diminished renin release and an intra-adrenal defect of a local renin-angiotensin system, both of which suppress aldosterone secretion.[1]

Hyporeninaemic hypoaldosteronism is a relatively common disorder in patients with mild diabetic and other forms of nephropathy, in particular those associated with non-steroidal anti-inflammatory drugs (NSAIDs).[2] Patients are often asymptomatic and present with hypertension despite diminished aldosterone levels, because of volume expansion in the presence of chronic kidney disease and normal levels of cortisol, which exhibits mineralocorticoid activity (MA). In our patient, chronic treatment with supraphysiological doses of prednisone caused Cushing's syndrome but also symptomatic tertiary adrenal insufficiency. In agreement, ACTH levels were suppressed but cortisol levels were within the normal range, which is most likely due to the interference of prednisolone (171% cross-reactivity) in the cortisol assay (Modular E170 immunoanalyser Roche Diagnostics, Germany). With the additional presence of hypoaldosteronism, MA is primarily dependent on the active prednisolone, which is converted out of prednisone by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). In contrast, 11β-HSD2 inactivates glucocorticoids,[3] which is more effective for prednisolone than for cortisol, explaining the reduced MA of prednisolone.[4]

Treatment with fludrocortisone, which is 125 times more potent than cortisol, rapidly improved the patient's well being, normalised blood pressure, and restored electrolyte concentrations and TTPG, which confirmed the diagnosis of adrenal insufficiency.

The combination of hyporeninaemic hypoaldosteronism due to diabetic nephropathy and chronic use of NSAIDs, suppression of endogenous cortisol secretion, and the negligible MA of prednisolone, resulted in symptomatic adrenal insufficiency.

Glucocorticoids given in supraphysiological dosages do not always display effective mineralocorticoid activity when symptomatic hypoaldosteronism is present. Therefore, when hyponatraemia and hyperkalaemia are not fully understood in a symptomatic patient, physicians should consider adrenal insufficiency, even in the presence of synthetic glucocorticoids.

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ANSWER TO PHOTO QUIZ (PAGE 529)

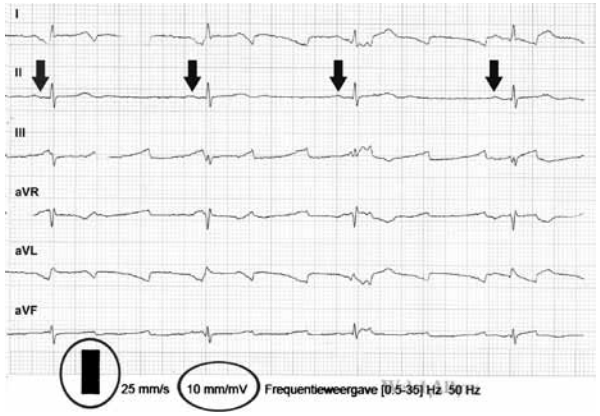
MARKED BRADYCARDIA IN A YOUNG WOMAN WITH WEIGHT LOSS

DIAGNOSIS

The ECG shows a sinus bradycardia with a slight sinus arrhythmia. Because of an artefact visible in the leads I, III, aVL and AVF, the bradycardia was thought to be due to a complete atrioventricular block with atrioventricular dissociation. Lead II, however, shows distinct atrial activity consistent with sinus bradycardia (*figure 2*). The presence of sinus P waves can best be examined in lead II because this lead is parallel to the electrical axis of a sinus P wave. An ECG is calibrated so that the 1-mV standardisation mark is 10 mm tall (*figure 2*, the two ovals). When atrial activity is unclear the standardisation can be doubled to make P waves more distinct.

Echocardiography showed no structural abnormalities and during treadmill exercise stress testing normal sinus tachycardia was obtained.

Figure 2. *Electrocardiogram with a sinus bradycardia*



The solid black arrows point out the sinus P waves in lead II. The standardisation mark as well as the calibration bar are encircled.

Sinus bradycardia is the single most observed arrhythmia in patients with malnutrition and weight loss, e.g. anorexia nervosa, and is found in almost 50% of the patients.[1,2] A marked sinus bradycardia with a heart rate of less than 40 beats/min is seen in 8 to 29% of patients with weight loss and was first described in 1966.[3] Other electrocardiographic findings are QT dispersion, ST and T-wave changes and diminished heart rate variability. A sympatho-vagal imbalance due to an increased parasympathetic activity is probably the mechanism that causes these electrocardiographic changes and sinus bradycardia can be considered a physiological adaptation to caloric deprivation.[4] Bradycardia in patients with anorexia nervosa generally resolves once a stable pattern of caloric intake and progressive weight gain is obtained. In this case the patient was admitted because of abdominal complaints, which were ascribed to an exacerbation of her IBS.

Case reports describe atrioventricular block, or ventricular arrhythmia, but these arrhythmias are particularly seen in patients with electrolyte disturbances e.g. hypokalaemia or hypomagnesaemia. In our case all laboratory analyses were within the normal range.

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ANSWER TO PHOTO QUIZ (PAGE 531)

A HAIRY PROBLEM

The organism was identified as a larva of *Clogmia albipunctata* (Williston, 1893) from the *Psychodidae* family, also known as owl flies, moth flies, or moth midges. *C. albipunctata* has been anecdotally associated with human myiasis mainly of the urogenital and nasopharyngeal tracts;[1,2] it has been identified as a hospital hygiene problem[3] and serves as a model for insect embryogenesis. It is a distant relative of insect vectors of various infectious diseases, including cutaneous leishmaniasis. This species originates from tropical and subtropical regions. However, since the mid-1990s, possibly via contaminated export fruit and vegetables and transported by planes and ships, *C. albipunctata* has been demonstrated in Europe.[4] It is a sewage dweller and frequently oviposits in latrines, toilets and more generally in (ecologically) nutrient-rich conditions. The larvae are versatile in their capacity to adapt to living conditions and feed on biofilms in any drain system. To prevent *C. albipunctata* from infesting and ovipositing, toilets and openings of waste pipes should be closed. Regular use of disinfectants is recommendable, as is anti-fly and anti-mosquito netting of bathroom and toilet windows.

The nuisance factor of infestation with *C. albipunctata* is considerable and patients may occasionally present with health concerns or even signs and symptoms of myiasis. In our case, larvae seem to have surfaced from the siphon of the bath tub when our traveller took a bath. Indeed, examination of consecutive menstrual secretions did not reveal moving living objects and our returning traveller remained free of symptoms suggestive of urogenital myiasis. Nonetheless, awareness of this pest and its possible implications if encountered in a health care setting is recommendable for hygienists, microbiologists and infectious diseases specialists.

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LETTER TO THE EDITOR

Comment to case report on intravascular lymphoma

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Dear Editor,

We read K. Boslooper's case report on intravascular lymphoma with great interest.[1] To our knowledge, intravascular lymphoma is rare, and may present as progressive multifocal cerebral infarction.[2] The diagnosis of intravascular lymphoma is difficult due to the non-specific presentation and lack of lymphadenopathy, thus leading to frequent instances of autopsy-proven diagnosis. However, in Boslooper's case, 18[F]-fluorodeoxyglucose (FDG)-PET was used as a powerful functional imaging tool to diagnosis. But some findings assessing the accuracy of FDG-PET in detecting this disease remain controversial. In several reports, FDG-PET was able to detect only two of seven pathologically confirmed lesions as positive FDG-PET findings and the number of tumour cells in pathological specimens tended to be high when FDG-PET and biopsy findings matched.[3]

We had a patient, a 40-year-old man, with weakness of his right limbs, impairment of his short-term memory, cognitive impairment, consciousness disturbance, seizure and fever of unknown origin (FUO). Brain magnetic resonance imaging (MRI) showed multiple cortical or subcortical lesions that were hypointense on T1-weighted images, hyperintense on T2 weight and fluid-attenuated inversion recovery (FLAIR) images, and irregular patchy areas with circular enhancement on enhanced images. Bacterial, fungal, and acid-fast bacilli cultures of the cerebrospinal fluid were negative. FDG-PET showed no abnormalities. Finally, postmortem examination revealed bilateral involvement of brain by large atypical lymphoid cells, mainly within the vasculature.

In conclusion, because appropriate treatment can improve clinical outcomes, timely and accurate diagnosis is extremely important for patients with this disease.[4] FDG-PET could, though, detect useful information leading to accurate diagnosis and prediction of severe complications, which could not be obtained using conventional diagnostic methods.[5,6] An important consensus on organ biopsies is mandatory for the accurate diagnosis of intravascular lymphoma.[7] Therefore, further studies are needed to establish the role of FDG-PET in this disease.

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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
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