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EDITORIAL

The challenge of Lyme disease: tired of the Lyme wars

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Few diseases have aroused more emotional attention in the press and the public than Lyme disease. Discussions have not only focused on the increasing incidence[1] or the choice of appropriate treatment, but also on perceived inadequacy of serological testing and whether or not persisting fatigue, cognitive dysfunction and musculoskeletal pain are 'real disease' and related to persistent infection. Large numbers of patients with such symptoms attributed to Lyme disease seek medical opinions, but no consensus on approach or treatment exists.

In this issue of the Journal, Coumou *et al.* provide a review on several aspects of Lyme disease.[2] This review is extremely helpful for understanding the epidemiology and immunopathogenesis of the disease. Does it also provide a framework for the Dutch physician confronted with a patient with putative Lyme borreliosis, as the authors state? Probably not, since this publication precedes and potentially contradicts the revised national CBO Treatment Guidelines for Lyme Disease, which will be published later this year. The CBO guidelines, initially released in 2004, have been subject of much debate.[3] Whereas the guideline recommendations on prevention and treatment of early Lyme disease – the easy part – have been generally accepted, the lack of recommendations for the approach to patients with persistent symptoms after standard treatment of short duration has been criticised. The difficult diagnosis and paucity of studies of sufficient quality on this subject have prompted the 2004 CBO Guidelines Committee to refrain from addressing this subject in depth. In contrast, in the pending 2011 revision of the guidelines, recommendations may be expected on the approach to the patient with chronic fatigue and other persistent symptoms attributed to Lyme disease, including algorithms on possible persistence and empirical or second-line therapy. Therefore, the views by Coumou *et al.* in the present issue of the Journal cannot be viewed as a therapeutic guide replacing the revised 2011 CBO guidelines, which were developed according to the recommendations for evidence-based development of guidelines by a multidisciplinary committee, including the National Society for Lyme Patients (NVLP).[4]

Therapy of early uncomplicated Lyme disease or erythema migrans is usually successful, and a short duration of therapy (10 to 15 days) leads to cure in 84 to 95% of cases.[5,6] Indeed, for the large majority of patients, if correctly diagnosed and timely treated, Lyme disease is not an insidious illness. Reported failure rates in patients with late manifestations, such as arthritis or acrodermatitis chronica atrophicans, are considerably higher[7,8] and little is known about treatment success rates among patients with a delayed diagnosis or initiation of treatment. Treatment success rates in the latter groups invariably do not reach 100%, underscoring the need for more research to try and understand what is wrong in patients with persistent signs or unexplained symptoms after standard therapy.

Whether long-term treatment may be helpful for patients with unexplained symptoms after standard therapy for Lyme disease is currently unknown. The randomised studies that have been performed have been of questionable quality and were heavily underpowered to detect potential effects. Several trials[9,10] were prematurely discontinued due to slow recruitment and were only partially published: e.g., the publication by Klempner *et al.* did not report the primary endpoint of success in the intent-to-treat population, but just reported results in evaluable subgroups as small as 22 to 35 patients. Thus, whereas these studies did not reveal statistically significant differences between treatment groups, they cannot serve to rule out an effect of antibiotic therapy, due to their lack of power and failure to report the predefined endpoints.[9,10] Indeed, other studies of variable quality have

suggested positive outcomes on some endpoints, such as persistent fatigue,[11] cognitive functioning[12] or treatment failures[13] in specific subgroups of patients with putative persistent infection, although these results were generally disappointing, and cannot be generalised.[11-13] Thus, there is a need for well-designed studies on this subject, rather than misusing outcomes of underpowered trials of disputed quality to either defend or deny the possible effect of antimicrobial therapy. A large randomised study to address this issue is currently being performed in the Netherlands.[14]

Serological testing for *B. burgdorferi* has been overemphasised, both by patients and physicians. Are these tests of abysmal quality, and are better serological tests available in other countries, as has been suggested in the lay press? Certainly not, but there is no need to conceal that the serological diagnosis of Lyme disease has its limitations.

As was demonstrated in a recent study from the Netherlands, the performance of serological assays is suboptimal.[15] In that study, eight commercially available ELISAs and five immunoblots were compared. The assays had a widely divergent sensitivity and specificity and a very poor concordance. ELISAs were positive in 34 to 59% of patients suspected of Lyme disease. Remarkably, there was very poor agreement between immunoblots, and their highly variable sensitivity and specificity further puts the much-advocated two-tier testing strategy into question. For example, a specific ELISA-immunoblot combination was able to confirm only 53% of positive ELISAs from patients suspected of Lyme disease, whereas another immunoblot confirmed 100% of the ELISA results.[15] These results underscore the notion that the outcome of serological testing is highly dependent on the commercial test kits chosen; hence the statement by Coumou *et al.* that serological tests have a 100% sensitivity for most manifestations of disease should be softened. This is not unusual, considering the fact that the development of a reliable test strategy for syphilis has required considerable efforts and is now based on a combination of tests, each with their own sensitivity, specificity and dynamics.

In addition, there is a clear need for the development of non-serology-based tests. Despite these shortcomings, not the quality of the assays but perhaps merely the incorrect interpretation of test results by both patients and physicians is the major hurdle. Importantly, as in many infections, antibodies persist for a long period of time, and possibly lifelong, after clinical cure of the infection.

Therefore, in addition to their limited sensitivity and specificity, it is clear that serological tests cannot be used to confirm or rule out the diagnosis of Lyme disease. Rather, serology may at most be helpful to increase or decrease the likelihood of disease in the context of the risk profile, the history, and the clinical signs and symptoms of an individual patient.

In their review, Coumou *et al.* provide a hypothetical case, in which the pre-test probability of Lyme disease is 0.5%. Not surprisingly, their calculations reveal that the predictive value of a positive test is very low. This confirms the textbook knowledge that screening tests for a disease with a likelihood of 0.5% are irrational. However, their example does not apply to patients with specific symptoms after a tick bite or erythema migrans, whose chance of having Lyme disease may be anywhere between 5 and 95%, depending on their individual situation.

Both patients and physicians should be aware of the limitations and the appropriate interpretation of serology, which is not different from many other infections. Thus, patients should not assume that the detection of antibodies indicates active infection. Likewise, physicians should not state that a failure to detect antibodies rules out disease. We have learned how to use a variety of tests, such as AST, Mantoux, Paul-Bunnel and Q-fever serology, with the cautious and professional interpretation of their limited predictive value, and we should be able to do so with Lyme serology, without misusing the results to convey personal viewpoints.

Why do doctors do their best to argue that patients consulting us about Lyme disease are overdemanding and should not be taken seriously? Clearly, many patients with aspecific symptoms do not have active Lyme disease, but this does not deny their concerns and their right to ask for a medical expertise. Patients with chronic fatigue and 'aspecific' symptoms, such as myalgia, impaired memory or concentration, headaches, or arthralgia, are often perceived as being annoying or overdemanding.[16] Most likely, doctors feeling insecure and powerless about patients with unexplained physical symptoms tend to blame their patients, especially if they express specific attributions and cognitions.

This leads to a strong tendency for circular reasoning, such as that stated by Coumou *et al.*: persistent infection as a cause of chronic symptoms after 'adequate treatment' is highly unlikely. Indeed, if 'adequate' signifies that the microorganism has been eradicated and the immune system has come to rest, the problem has been solved, but the issue rather is whether treatment has been 'adequate' or not in patients who continue to feel ill. In fact, authors using the term 'adequate treatment' suggest to be certain without further study that treatment has been successful and curative in 100% of cases, while actually referring to standard therapy for uncomplicated disease.

Likewise, designating such patients as having 'post-Lyme disease syndrome' (PLDS) incorrectly suggests a prior knowledge that the disease has been cured ('post' meaning after), before reasonable attempts have been

made to rule out relapse or persistent infection. Whereas persistent infection may be highly unlikely in many patients, using deceitful terminology hampers a scientific and evidence-based approach. For this reason, the Dutch CBO 2011 Guidelines Committee has recommended not to use the term PLDS.

We agree with Coumou *et al*. that the term 'chronic Lyme disease' for persistent symptoms after so-called 'adequate' therapy is inappropriate, but this diagnosis cannot be rejected without a reasonable assessment whether patients do have persistent infection, post-infectious complaints, or rather a syndrome unrelated to Lyme disease. There are many diagnoses in infectious diseases, ranging from urinary tract infection to *Staphylococcus aureus* septicaemia, and from syphilis to Q-fever, where failure of primary therapy or late recurrences do occur in a minority of patients. There is general agreement that such patients deserve medical evaluation to rule out a potential relapse when having persistent or recurrent symptoms, and the approach to infection with *B. burgdorferi* should not be different. There is no place for circular reasoning ('Your treatment has been "adequate", so you can't have symptoms') or exaggerated assumptions ('standard therapy never fails', or 'our serological assay is 100% sensitive').

Does this mean that all patients presenting with chronic fatigue and arthralgias have persistent *Borrelia* infection? By no means, persistent infection by *B. burgdorferi* is probably rare, and many patients seeking information on Lyme disease most likely do not have a persistent infection. This is not different from the notion that not all patients presenting with a nodule have cancer, and not all patients with a sore throat have streptococcal angina.

Patients with chronic fatigue and persistent symptoms after having had a *B. burgdorferi* infection are persons who seek help and should not be turned away at the doorstep. We as doctors should not blame them for our limited capacity to address unexplained physical symptoms.

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REVIEW

Tired of Lyme borreliosis

Lyme borreliosis in the Netherlands

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ABSTRACT

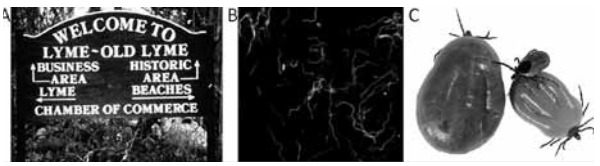
Lyme borreliosis has become the most common vector-borne illness in North Eastern USA and Europe. It is a zoonotic disease, with well-defined symptoms, caused by *B. burgdorferi* sensu lato, and transmitted by ticks. Lyme borreliosis is endemic in the Netherlands with a yearly incidence of approximately 133 cases/100,000 inhabitants. Similar to another spirochetal disease, syphilis, it can be divided into three stages; early, early disseminated and late disseminated manifestations of disease, of which the specific clinical presentations will be discussed in detail. The diagnosis of Lyme borreliosis is based on a history of potential exposure to ticks and the risk of infection with *B. burgdorferi* s.l., development of specific symptoms, exclusion of other causes, and when appropriate, combined with serological and/or other diagnostic tests. The specific indications for, but also the limitations of, serology and other diagnostic tests, including the polymerase chain reaction (PCR), are detailed in this review. Lyme borreliosis is treated with antibiotics, which are usually highly effective. Recent literature discussing the indications for antibiotic treatment, the dosage, duration and type of antibiotic, as well as indications to withhold antibiotic treatment, are reviewed. This review presents the most recent, and when available Dutch, evidence-based information on the ecology, pathogenesis, clinical presentation, diagnosis, treatment and prevention of Lyme borreliosis, argues against the many misconceptions that surround the disease, and provides a framework for the Dutch physician confronted with a patient with putative Lyme borreliosis.

Keywords: Lyme borreliosis, *B. burgdorferi*, clinical signs, diagnostics, treatment

INTRODUCTION

Lyme disease, or Lyme borreliosis, has become the most common tick-borne disease in North Eastern USA and Europe.[1] The disease is named after the town Old Lyme, Connecticut, USA (*figure 1A*), where the link between a tick-borne disease and a group of children suspected of juvenile arthritis was noted in the mid-1970s.[2] Seven years later, the causative agent was discovered by Burgdorfer.[3] In Europe, syndromes, reported as early as 1883, among which Bannwarth syndrome (painful radiculitis, cranial neuritis and lymphocytic meningitis), can retrospectively be designated as manifestations of Lyme borreliosis.[4,5] Lyme borreliosis is caused by spirochetes of the *Borrelia burgdorferi* sensu lato (s.l.) group *(figure 1B)*.[3] In the USA, *Borrelia burgdorferi* sensu stricto, from here on referred to as *B. burgdorferi,* is the sole causative agent, whereas in Europe *Borrelia garinii* and *Borrelia afzelii* are the predominant causative agents and to a lesser extent *B. burgdorferi* and more recently also *Borrelia bavariensis* and *Borrelia spielmanii*.[6,7] More *Borrelia* species, for example *Borrelia valaisiana* and *Borrelia lusitaniae,* have been identified in Europe; however, for most of these species the pathogenicity to humans is not as clear.[8] In 2009,

Figure 1. *Introduction to Lyme borreliosis*



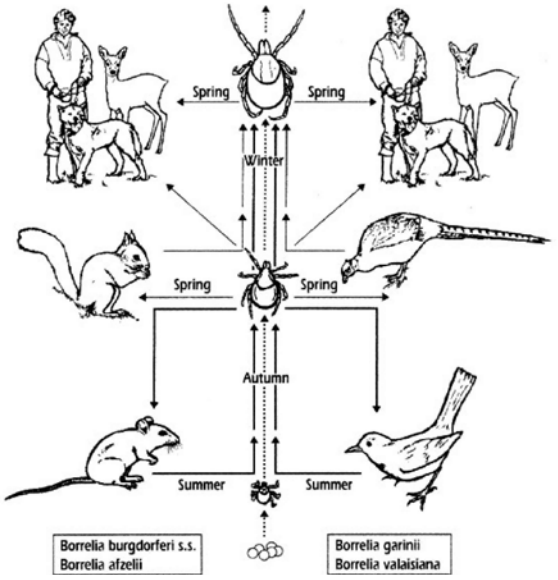
A. The little town, Old Lyme, Connecticut, USA. *B. Fluorescence* microscope image of the spirochete B. burgdorferi. C. Flat, partially fed and fully engorged *Ixodes ricinus* ticks.

Dutch general practitioners (GPs) were estimated to have diagnosed early Lyme borreliosis 22,000 times, corresponding with approximately 133 new cases of erythema migrans (see below) per 100,000 inhabitants per year. This number increased from 6500 in 1994, 13,000 in 2001 to 17,000 in 2005.[9,10]

ECOLOGY

In the USA *B. burgdorferi* is transmitted by the deer tick, *Ixodes scapularis*, whereas the European *Borrelia* species are transmitted by the sheep tick, *Ixodes ricinus (figure 1C)*. In general, uninfected tick larvae acquire the bacterium by feeding on infected animals. Ticks remain infected during their consecutive moulting periods, enabling both nymphal and adult ticks to transmit spirochetes to other (larger) animals, including humans. After their final blood meal adult female ticks, which have already mated, usually lay uninfected eggs *(figure 2)*.[11] The number of visits to Dutch GPs for tick bites rose from 371 per 100,000 in 2001, to 446 and 564 in 2005 and 2009, respectively.[9] In the Netherlands roughly 20% of adult ticks are infected, compared with 10% of nymphs, as shown by a European meta-analysis in 2005.[12] In 2007, 38% of all tick bites in the Netherlands happened in forests, 36% in gardens and 10% in dunes.[13]

Figure 2. *Simplified diagram of the transmission cycle of B. burgdorferi sensu lato species in the Netherlands*



***Borrelia* transmission is tightly interwoven with the tick reproductive cycle, which is estimated to take two years in the temperate climate zone. Uninfected eggs (vertical transmission, represented by the thin dashed line, seldom occurs) hatch in summer and autumn and larvae feed in autumn before, or in spring, after winter diapause. In early spring the largest cohort of nymphal ticks emerges, which may yield adult ticks in summer and autumn. In spring young hosts are infected by the emerged nymphs creating the possibility for larvae to acquire an infected blood meal which in its turn augments the abundance of infected nymphs (thick continuous lines 'spring' and 'summer'). On the right side of the diagram the cycle depicts the flow of *Borrelia* though avian populations (mainly *B. garinii* and *B. valaisiana*), while on the left side the flow of *B. burgdorferi* sensu stricto and *B. afzelii*, both with preference for mammals, is shown. However, all four species may be transferred by nymphal and adult ticks (thin continuous lines) to large hosts such as deer, dogs and humans. We thank Dr KE Hovius for providing the figure.**

PATHOGENESIS

Borrelia encounters different environments during its enzootic life cycle,[14] for which differential expression of outer surface proteins (Osp's) is crucial. In unfed ticks, spirochetes express OspA, which binds to the tick receptor of OspA (TROSPA), ensuring attachment of the spirochete to the tick gut.[15] In feeding ticks, approximately 24 to 48 hours after attachment, *Borrelia* down-regulates OspA, expresses OspC and migrates to the salivary glands.[16,17] Here, OspC binds a tick salivary gland protein of 15 kDa (Salp15), shielding the spirochete from complement-dependent (antibody-mediated) killing when transmitted to the host.[18-20] Furthermore, we have previously shown that Salp15 exerts immunosuppressive activity;[21] inhibiting murine T-cell activation and suppressing human dendritic cell (DC) function,[22] which could facilitate both tick feeding as well as *Borrelia* transmission. Numerous other tick proteins, which interact with other host defence mechanisms, facilitate tick feeding and/or enhance the transmission of *Borrelia* or other tick-borne pathogens from the tick to the host, have been identified, as we have previously reviewed.[23] Furthermore, a number of adhesins, proteins on the outer membrane of *B. burgdorferi* s.l. that are involved in the anchoring and interaction with host cells, have been identified, and are important for the establishment and dissemination of infection.[24]

A striking feature of *Borrelia* is its ability to evade host immune response. One mechanism to evade host immune responses is the recombinant gene expression of the variable major protein-like sequence (*vls)* locus.[25] This results in altered antigenicity of the lipoprotein VlsE and thus protection against anti-VlsE antibodies.[26] Also, *Borrelia* can express complement regulator-acquiring surface proteins (CRASPs), preventing complement-mediated killing.[27,28] Recently, another protein, Lmp1, was suggested to be important for evasion of the host adaptive immune responses. Yang *et al.* showed that the N-terminal region of the protein increased pathogen survival.[29] Importantly, *B. afzelii* is associated with skin manifestations, *B. garinii* with neurological involvement and *B. burgdorferi* with infection of the large joints; however, there is a fair amount of overlap between the tropisms of the different genospecies.[30]

CLINICAL MANIFESTATIONS

Tick bite

In a Dutch study with 167 tick bite cases in a GP population, only one case (0.7%) developed Lyme borreliosis upon follow-up serology. Notably, this tick was attached longer than 24 hours.[31] In general, ticks attached shorter than 24 hours do not transmit *Borrelia*.[32,33] Erythematous skin lesions smaller than 5 cm starting within two days after detachment of the tick are most likely a tick bite hypersensitivity reaction. Tick bite hypersensitivity should disappear within one to two days. Diagnostic tests or treatment after a possible tick bite, without symptoms of early Lyme borreliosis (see below), are not recommended in the Netherlands.[34] A recent meta-analysis suggested that, in highly endemic areas in the United States, one case of Lyme borreliosis is prevented for every approximately 50 individuals who are prophylactically treated with antibiotics.[35] Importantly, asymptomatic infection is thought to be much more frequent in Europe than in the USA,[36] arguing against the standard use of prophylactic antibiotics after a tick bite in Europe. However, in individual cases, when the tick was acquired in a highly endemic area of the Netherlands (see www.rivm.nl/cib/infectieziekten-A-Z/infectieziekten/Lyme-borreliose), was attached for a longer period of time, i.e. more than 24 to 48 hours, and the patient presents within three days after the tick bite, prophylactic doxycycline (200 mg once) can be considered. Patient instructions to be alert for typical symptoms of (early) Lyme borreliosis (see below) might be an equally effective alternative.

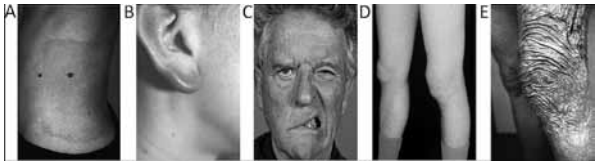
Early Lyme borreliosis (days to weeks)

Typical erythema migrans is an expanding erythematous skin lesion with central clearing located at the site of tick bite starting after three to 30 days, typically after seven to 14 days, which can vary from 5 to 75 cm (median 15 cm) *(figure 3A)*.[37] Both systemic symptoms, such as fever, myalgias and arthralgias, and local symptoms among which itching, burning, and mild pain can accompany EM. A borrelial lymphocytoma is seldom diagnosed, and only in Europe, and described as a bluish red tumour-like skin infiltrate, often located at the earlobe *(figure 3B)* or nipple. It is more common in children and can spontaneously resolve.[6,38] Early Lyme borreliosis symptoms respond well to antibiotic therapy.[39] In Europe, 77 to 89% of all Lyme manifestations are erythema migrans and 2 to 3% borrelial lymphocytoma.[40,41]

Early disseminated Lyme borreliosis (weeks to months)

When the infection is untreated, the spirochete can disseminate and cause early neuroborreliosis (3-16% of Lyme manifestations), Lyme arthritis (5-7%), and seldom a (myo)carditits with (partial) atrioventricular block (<1%).[40,41] Notably, since the late 1980s, increasing awareness for EM and better effective antibiotic regimes have probably made these clinical manifestations become even less common.[42] The European Union Concerted Action on Lyme borreliosis (EUCALB, www.eucalb.com) has established criteria for these manifestations for clinical purposes, which are used in the Dutch guideline developed by the Dutch Institute for Healthcare Improvement (CBO) in 2004,[34,43] which is currently being updated. Early neuroborreliosis can present with lymphocytic meningitis, which is more common in the United States, cranial nerve paresis, usually the facial nerve *(figure 3C)*, painful radiculitis, which is more common in Europe, or all of the above, which is equivalent to the Bannwarth syndrome.[44,45] In most patients, acute neurological symptoms improve or resolve in several weeks to months, even without antibiotic treatment.[42] In the early disseminated phase of Lyme borreliosis, infection of the joints is oligoarticular and 50% occur in the knee *(figure 3D)*. This manifestation is mostly observed in the United States, where 60% of untreated patients developed arthritis.[42] Cardiac involvement in early Lyme borreliosis in adults is rare and symptoms are usually related to atrioventricular conduction abnormalities.[36]

Figure 3. *Clinical symptoms of Lyme borreliosis*



A. Erythema migrans B. Borrelial lymphocytoma C. Facialis paresis D. Lyme arthritis. E. Acrodermatitis Chronica Atrophicans late (atrophic) stage. We are grateful to Prof. Dr. A.C. Steere and Dr. D.J. Tazelaar for the pictures.

Late Lyme borreliosis (months to years)

One could divide late Lyme manifestations into two groups, manifestations in which persistent *Borrelia* infection is causative for the ongoing symptoms, e.g. acrodermatitis chronica atrophicans (ACA), persistent (untreated) Lyme arthritis and neuroborreliosis, and manifestations in which other mechanisms, e.g. autoimmune phenomena or irreversible tissue damage, might play a role, such as antibiotic-refractory Lyme arthritis, encephalopathy (a subgroup of late neuroborreliosis) and dilated cardiomyopathy.[36] Importantly, over half of the patients with late manifestations of Lyme borreliosis do not remember an EM.[44,46]

ACA can develop up to ten years after infection and is described as a bluish-red atrophic skin lesion, initially combined with oedema, in later stages with atrophy *(figure 3E)* and is predominantly located on the plantar sites of

hands and feet or distal parts of the legs. Periarticular nodules, sclerotic lesions and sensory polyneuropathy can be observed.[47] ACA can be confused with vascular conditions, such as venous insufficiency, particularly when the legs are affected.[48] It generally occurs in women older than 40 years,[49] but has been described incidentally in children.[50]

Late neuroborreliosis is rare and includes encephalomyelitis, encephalopathy and axonal polyneuropathy, for a period of at least six months.[42] Encephalomyelitis can present as a slowly progressive myelopathy beginning with an ataxic gait, a gradually worsening spastic paraparesis or tetraparesis or with hearing loss and is accompanied by relatively severe cerebrospinal fluid (CSF) pleocytosis or evident intrathecal anti-*Borrelia* antibody production.[44,51] In contrast, symptoms of encephalopathy are mainly cognitive, in combination with aspecific symptoms, such as fatigue, malaise and myalgia. In most of these patients, there is no evidence of inflammation due to *Borrelia* in the central nervous system (CNS), and therefore, an encephalopathy might actually be an indirect effect of systemic (non-CNS) infection accompanying typical clinical findings of disseminated Lyme borreliosis.[52] Finally, an European study showed that isolated chronic polyneuropathy, without the presence of other late Lyme borreliosis manifestations, such as ACA, is rarely caused by *B. burgdorferi* s.l. infection.[53]

Joint manifestations can occur months to years after exposure, with intermittent recurrent attacks that persist for days, weeks, or months and are typically asymmetrical and pauciarticular in nature and involve one or two larger joints and almost invariably the knee.[54] Most Lyme arthritis patients respond well to conventional antibiotic treatment strategies, such as doxycycline, but a small percentage will continue to have chronic joint inflammation, not due to persistence of the spirochete. This is called antibiotic-refractory Lyme arthritis and occurs more often in the United States than in Europe[42] and has recently been associated with polymorphisms in toll-like receptor (TLR)-1[55] and autoantibodies[56] (and personal communication Prof. Dr. A.C. Steere, Harvard Medical School, Boston, Massachutes, USA), genetic predisposition, i.e. the presence of certain HLA-DR alleles,[57] specific *B. burgdorferi* genotypes[58] and T cell responses, i.e. Th17 responses[59] and low number of regulatory T cells.[60]

In dilated cardiomyopathy, a very rare manifestation of late Lyme borreliosis, spirochetes have rarely been isolated by culture. This might indicate that symptoms could be due to past infection and myocardial scarring rather than ongoing inflammation due to the presence of the spirochete.[61]

A large proportion of treatment-naive individuals present with serological evidence of exposure to *B. burgdorferi* s.l. and symptoms that are aspecific and highly prevalent in the normal population, such as fatigue, myalgia, headache and joint pain. These are not considered specific symptoms or signs of late Lyme borreliosis. However, a selection of these individuals might have an increased risk of Lyme borreliosis, for example a history of previous EM or abundant tick infestations, or live in a highly endemic region of the Netherlands. Although these aspecific symptoms are highly prevalent in the normal population, as are antibodies against *Borrelia* (see below), when other causes have been thoroughly excluded the diagnosis Lyme borreliosis could be considered in a minority of these individuals.

Persistent aspecific symptoms after treatment

A minority of patients, approximately 10 to 20%,[62] experience aspecific symptoms after adequate treatment with antibiotics. This complex of aspecific symptoms might best be referred to as post-Lyme disease syndrome (PLDS).[63] PLDS, for which a definition has been postulated,[37] has been linked to a broad array of symptoms that are highly prevalent in the normal population,[64] similar to those described in the last paragraph of the previous section. This, in combination with the fact that specific antibodies against *Borrelia* occur in approximately 4 to 8% of the normal Dutch population,[65] and in even up to 20% in highly endemic areas in other European countries,[66] and the fact that in this group additional antibiotics after previous adequate treatment have no substantial beneficial effects compared to placebo,[67-70] strongly suggests that persistent *Borrelia* infection is not the cause of the symptoms. Indeed, in animal models (mouse and dog), *B. burgdorferi*-infected animals readily become culture negative upon antibiotic treatment.[71,72] In these studies, which all have major pharmacodynamic concerns, persistence of *B. burgdorferi* DNA has been reported, but has not been associated with disease.[36,73] In humans, mostly in studies of questionable quality and in studies that did not use recommended courses of antibiotic treatment, treatment failure – importantly often associated with persistence or development of specific symptoms – has been described.[74-77] In contrast, in well-designed studies using recommended therapies treatment failure is only seldom reported.[39,78,79] Therefore, the term 'chronic Lyme disease' for persistent aspecific symptoms after adequate treatment for Lyme borreliosis seems to be a misnomer and should be avoided.[63]

DIAGNOSTICS

Considerations before diagnostic tests are performed

The diagnosis of Lyme borreliosis is predominantly based on clinical symptoms and serological tests. The diagnosis can be readily considered in case of symptoms which have been associated with *Borrelia* infection and serological evidence for *Borrelia* infection *(table 1)*. However, in the

Table 1. *Overview of recommended diagnostics and treatment for the different manifestations of Lyme borreliosi*

Clinical manifestation	Serum antibodies sensitivity[I]	Other helpful diagnostics	Sensitivity other diagnostics[VI]	Treatment CBO (2004) and IDSA (2006) first choice	Treatment alternatives
Erythema migrans	38-88% > 6 weeks: 100%[137]	*In case of atypical EM*[IV] PCR Culture	60-80%[90-92] 40-88%[93,94]	Doxycycline bid 100 mg for 10-14 days	Amoxicillin tid 500 mg for 14 days[VII] or azithromycin qd 500 mg 5 days
Borrelial lymphocytoma	70%	Histopathology PCR Culture	ND 24%[95]	Doxycycline bid 100 mg for 10-14 days	Amoxicillin tid 500 mg for 14 days[VII] or azithromycin qd 500 mg 5 days
Early neuroborreliosis	80% > 6 weeks: 100%	Intrathecal antibodies (AI) LP cell count (pleocytosis) LP culture LP PCR	55-80%[98,99] 95-100%[44,138] 13%[110] 10-50%[102-104]	Ceftriaxone qd 2 gram[IV] for 14 days	Penicillin-G 2-3 ME 6 times a day, for 14 days or Doxycycline bid 200 mg for 14 days[97]
Late neuroborreliosis	100%	Intrathecal antibodies (AI) LP cell count (pleocytosis)	100%[44] 100%[34,44,139]	Ceftriaxone qd 2 gram[IV] for 30 days	Doxycycline bid 100 mg for 30 days[VIII]
Lyme arthritis	100%[II]	Synovial fluid PCR	46-88%[89,107]	Doxycycline bid 100 mg for 30 days	Ceftriaxone qd 2 gram iv for 14 days
Lyme carditis	80-100%[III]	ECG[V]	ND	Doxycycline b.i.d 100 mg for 21 days	Ceftriaxone q.d 2 gram[IV] for 14 days
Acrodermatitis chronica atrophicans (ACA)	100%	Histopathology PCR Culture	68-92%[91,92] 22-60%[88]	Doxycycline b.i.d 100 mg for 21-30 days	Ceftriaxone q.d 2 gram[IV] for 14 days[127]

I: Based on the CBO guideline 2004, IDSA guideline 2006. Since 4-8% of the normal population has antibodies against Borrelia, the theoretical specificity of serology is limited to 92-96%. II: Borrelia serology only recommended if the knee is involved. III: Estimated to become 100% during the course of the disease based on other disseminated manifestations. IV: Serology is recommended at least 6-8 weeks after onset. V: Only perform in case of proven early disseminated Lyme borreliosis. VI: In theory, specificity of culture is 100%, of PCR (when appropriate measures are undertaken) 93-100%, and AI 63-97%. VII: In case of pregnancy, photosensibility or allergy for doxycycline. VIII: In case of absence of pleiocytosis. ND: no data. This table does not include treatment recommendations for children younger than 9 years. EM = erythema migrans; PCR = polymerase chain reaction; ND = no data; AI = antibody index; LP = lumbar puncture; qd = once daily; bid = twice daily, tid = three times a day; iv = intravenous.

absence of specific clinical symptoms, the presence of anti-*Borrelia* antibodies does not necessarily indicate the presence of an active *Borrelia* infection, since 4 to 20% of the normal Western European population have detectable antibodies,[65,66,80] most likely due to an (asymptomatic) *Borrelia* infection in the past. When antibodies against *Borrelia* are detected in individuals without specific clinical symptoms, these could be considered 'false positive', since they are not predictive of disease. Therefore, international guidelines, including the CBO 2004 guideline,[34,37] recommend not to test for antibodies against *Borrelia* when there is only a small suspicion on Lyme borreliosis. This has been recently reviewed by others[81] and is enumerated in *table 2*. Despite these recommendations, we have recently shown that of all serological tests (n=312) requested by Dutch physicians in the Amsterdam area, 72% are from individuals with aspecific symptoms. Not surprisingly, in 6% of these sera we demonstrated antibodies against *B. burgdorferi* s.l. (unpublished data), which equals the seroprevalence of the Dutch population.

Table 2. *Testing for antibodies against B. burgdorferi in the normal population*

Test	Lyme disease	No Lyme disease	Total
Positive	40	497	537
Negative	10	9453	9463
Total	50	9950	10,000

False positives = (497/537) *100 = **92.5%**
False negatives = (10/9463) *100 = **0.1%**

Sensitivity: 80%; specificity 95%, pre-test probability: 0.5%. Sensitivity and specificity are based on published literature (see text). The pre-test probability is an estimation based on recent RIVM data and the percentual distribution of symptoms of Lyme borreliosis.

General considerations on diagnostic tests

Detection of antibodies in serum directed against *B. burgdorferi* s.l. is the most common diagnostic approach. Several guidelines recommend that (at least second generation) *B. burgdorferi* s.l. Enzyme-linked Immuno Sorbent Assays (ELISAs or EIAs) should be used as a screening test and, when reactive, should be confirmed by an immunoblot or Western blot (two-tier testing).[34,82] The spectrum of *Borrelia* proteins recognised on Western blot expands with the duration of symptoms.[82] A European multicentre study has indicated eight bands suitable for diagnostic purposes.[83] Compared with IgG, the specificity of IgM components is lower, since rheumatoid factor, acute Epstein-Barr virus (EBV), cytomegalovirus (CMV)

infection, multiple sclerosis and other autoimmune diseases can also give a false-positive test.[82,84,85] Newer serological tests include an ELISA detecting antibodies against C6, a 26-amino acid peptide that reproduces the sequence of the sixth invariable region (IR6) within the central domain of the VlsE protein of *B. burgdorferi* s.l.[86] Despite these new developments, two-tier testing is still considered to be necessary, since the immunoblot has a higher specificity than ELISA or EIA. However, in the very early stages of Lyme borreliosis, the immunoblot can be false negative.[86,87] Recently, Branda *et al.* proposed a new testing strategy, two-tiered IgG testing, which avoids the use of IgM blots. Compared with the standard two-tier testing, this method had significantly better sensitivity in early disseminated Lyme borreliosis, the same sensitivity in early and late Lyme borreliosis and a comparable specificity.[87] Other validated and widely accepted diagnostics include culture and polymerase chain reaction (PCR).[34] Clearly, a positive culture in the presence of ongoing specific symptoms indicates an active infection and should be considered as the 'gold standard'. Unfortunately, there are limitations to culture.[36] It is expensive, tissue samples should be incubated in special medium for weeks and there is limited availability in the Netherlands.[34] Sensitivity of culture and PCR to detect *Borrelia* in different tissues/fluids during the different stages of Lyme borreliosis is highly variable (*table 1* and see below). In theory, specificity for culture is 100%. Overall specificity for PCR is 93 to 100%,[88-90] provided certain measures are undertaken to avoid contamination, and amplified products are specified by an appropriate method, e.g. sequencing.[82]

Diagnostic tests for Lyme borreliosis manifestations

Early Lyme borreliosis. EM is a clinical diagnosis and serological tests are not necessary and not recommended *(table 1)*. In case of atypical EM and borrelial lymphocytoma, serological testing can be considered at least six to eight weeks after onset of symptoms *(table 1)*.[34] Alternatively, during these cutaneous manifestations, a skin biopsy at the margins of the EM could be considered for PCR or culture, for which sensitivities of 60 to 80%[90-92] and 40 to 88%,[93,94] respectively, have been reported. Culture for borrelial lymphocytoma has a sensitivity of 24%.[95] Antibiotic treatment during early phases of infection cause a decrease in antibody titres against *Borrelia*.[96]

Early disseminated Lyme borreliosis. Because clinical aspects of early disseminated Lyme borreliosis are not as visually clear as EM and have a broader differential diagnosis, laboratory evidence is necessary *(table 1)*. A guideline from Mygland *et al.* in 2010 provides recommendations for the diagnosis and treatment of neuroborreliosis in Europe.[97] To demonstrate intrathecal production of anti-*Borrelia* antibodies, the cerebral spine fluid (CSF)/serum antibody index (AI) should be performed. Early in the course of neuroborreliosis, absent pleocytosis in CSF has been described and sensitivity of AI is around 55 to 80%.[98,99] After six weeks of symptoms the sensitivity of AI approximates 100%.[100] The specificity of AI has not been the topic of extensive investigation, but ranges from 63[101] to 97%.[98] Several studies have shown a sensitivity of 10 to 50% for the PCR on CSF during early neuroborreliosis.[102-104] PCR on CSF could be useful when there is a strong suspicion of neuroborreliosis and the AI is negative or in patients with an immunodeficiency.[97] Indeed, in a recent patient, who presented to our medical department with a history of tick exposure and symptoms compatible with early neuroborreliosis, we demonstrated the presence of *Borrelia* DNA in CSF by PCR, without the presence of specific anti-*Borrelia* antibodies in serum or CSF. Importantly, this patient had previously been treated with chemotherapy for T-cell lymphoma and was receiving Rituximab, an anti-CD20 monoclonal depleting B-cells, which could explain the absent antibody response (unpublished data). More often, anti-*Borrelia* antibodies are found in CSF, but patients have other neurological diseases. This is illustrated by a study in which, of in total 123 patients with positive *Borrelia* serology (IgG) in CSF, 74 patients had another aetiological diagnosis.[98] Recently, the chemokine CXCL-13 in CSF has been shown to be a promising future diagnostic/treatment marker for neuroborreliosis.[105,106] Both early Lyme arthritis and myocarditis have a broad differential diagnosis and other causes need to be excluded. This, combined with a low a priori change when other Lyme borreliosis manifestations are absent, results in a low positive predictive value for positive antibodies. Therefore, especially for Lyme arthritis, other diagnostic tests such as PCR on synovial fluid should be considered *(table 1)*. PCR of synovial fluid has a sensitivity of 46 to 88%.[89,107] Notably, antibodies are present in 100% of Lyme arthritis and in 80% of Lyme myocarditis cases *(table 1)*.

Late disseminated Lyme borreliosis. Patients with ACA have detectable antibodies in 100% of the cases, the sensitivity of PCR on ACA skin biopsy ranges from 68 to 92%,[91,92,108,109] whereas culture has a lower sensitivity ranging from 22 to 60%.[88] For late neuroborreliosis, criteria include symptoms suggestive of late neuroborreliosis – no other obvious reason for the presenting symptoms, pleocytosis, and demonstration of intrathecal specific antibody synthesis (AI). In late neuroborreliosis, antibodies are present in 100% of the cases, but PCR and culture have a low sensitivity,[97,110] and are therefore not recommended (*table 1*). Late Lyme arthritis also has a 100% antibody detection rate. Routine screening of patients

with idiopathic dilated cardiomyopathy for antibodies against *B. burgdorferi* s.l. is of limited utility and should be reserved for patients with a clear history of antecedent Lyme borreliosis symptoms or tick bite.[111]

Invalidated or not recommended diagnostics

Over the last few years Lyme borreliosis has attracted a lot of media attention. By some, an image is created of an insidious (almost) incurable disease, which is extremely difficult to diagnose and for which current diagnostic tests are totally useless. This has created a ground for commercial laboratories offering invalidated or not recommended diagnostic tests. By some, blood and urine are offered for the detection of *Borrelia* DNA. PCR on these body fluids is not validated and not recommended for microbiological diagnosis.[82] A meta-analysis showed a wide range in sensitivity of the urine *Borrelia* PCR of 13 to 100%.[112] A study showed that, after establishing an optimal PCR protocol with spiked urine, *Borrelia* DNA was detected in only one of 12 patients with an acute infection (EM).[113] PCR on blood has a poor sensitivity of only 10 to 18%[88,104,114,115] and there are no European studies performed with a good control group, thus the specificity remains unclear. Theoretically, the specificity should be 100%; however, as outlined before, it is of paramount importance that (commercial) laboratories avoid DNA contamination, perform the correct controls and validate their PCR amplicon. A prospective controlled, blinded study from the USA in 1995 reported a sensitivity of PCR on blood of 18.4% in patients with EM.[114] Blood microscopy should not be used for diagnosis.[37] In addition, in a study using healthy volunteers as a control group, elevated complement factors, such as C3a and C4a, have been associated with acute and chronic Lyme disease.[116,117] These factors will be elevated in many other medical conditions and should therefore not be used to diagnose Lyme disease. Finally, diminished expression of CD57 on mononuclear cells has been claimed to be associated with PLDS.[118] In this study HIV-infected individuals were used as a control group. In HIV infection it has been shown that CD57 expression is upregulated,[119] making it impossible to draw conclusions from this study, and others could not confirm this finding.[120] Finally, commercial laboratories offer PCR to determine if attached ticks are infected with *Borrelia*. This is not recommended by the guidelines, since a positive PCR is not predictable for infection.[121]

THERAPY FOR SPECIFIC LYME BORRELIOSIS MANIFESTATIONS

Antibiotics are effective in all manifestations of Lyme borreliosis *(table 1)*.[42] The difference between antibiotics and expectative policy for EM has never been studied, because the justified use of antibiotics has been shown by randomised double-masked trials in which different antibiotics were compared. However, in theory, in analogy with other manifestations of Lyme borreliosis and other spirochetal diseases such as syphilis, EM could spontaneously resolve. For early Lyme borreliosis manifestations, such as EM and borrelial lymphocytoma, oral treatment, i.e. ten to 14 days of doxycycline, is as effective as parental antibiotics,[122] but has lower risks and adverse events. Importantly, two randomised double-masked trials support a ten-day course of doxycycline 100 mg twice daily.[123,124] Finally, a recent European trial confirmed that oral treatment of early Lyme borreliosis is successful in almost 100% of the cases. Moreover, in the unlikely event of treatment failure (0.4 to 0.7%), objective symptoms of Lyme borreliosis occurred. Importantly, not only were the newly developed aspecific symptoms in the treated EM group comparable with those in the treated age- and sex-matched control group, also the frequency of these symptoms was identical in both groups.[78]

For early disseminated Lyme borreliosis doxycycline is also recommended, except for neuroborreliosis with CNS manifestations, for which ceftriaxone iv is the treatment of choice *(table 1)*. Notably, a multicentre double-blind randomised trial compared ceftriaxone iv with oral doxycycline for adults with (early) neuroborreliosis and concluded that both are equally effective.[125] Although older open studies have suggested that longer treatment, i.e. longer than the recommended 14 to 30 days, might be justified for early (and late) disseminated Lyme borreliosis, a multicentre placebo-controlled randomised trial has shown that prolonged treatment of both early and late disseminated Lyme borreliosis is not warranted,[126] which is in line with most, if not all, esteemed and peer-reviewed international guidelines.[37]

In late manifestations of Lyme borreliosis, the same antibiotics are recommended, but with a longer duration of treatment (*table 1*).[127] For selected individuals with aspecific symptoms in combination with positive Lyme serology antibiotic treatment could be considered. Although, to our knowledge, evidence-based guidelines for this are non-existent, treatment could be adjusted based on the duration of symptoms, e.g. short duration of symptoms (<3 months) could be treated with 10-14 days of doxycycline 100 mg twice a day and longer lasting symptoms with 30 days of doxycycline 100 mg twice a day.

In case of persistence of specific Lyme borreliosis symptoms, persisting *B. burgdorferi* s.l. infection, or re-infection, should be considered and additional or prolonged therapy could be indicated. In stark contrast,

patients with PLDS, or individuals with false-positive Lyme serology and aspecific symptoms, such as fatigue, myalgia, headache and joint pain, should not receive antibiotic treatment. However, some of these patients are occasionally unjustly treated for months to years with (multiple) intravenously administered antibiotics, for which no credible scientific evidence exists. Such approaches pose a great risk for serious adverse effects.[68,69] As stated before, multiple placebo-controlled randomised trials have shown no substantial additional effect for additional antibiotic treatment in these individuals.[67-70]

PREVENTION

The best preventive method to prevent *Borrelia* infection is to attempt to avoid exposure to ticks by wearing protective clothing. In addition, a full body check within 24 hours after possible tick exposure could detect attached ticks, which should be promptly removed. This strategy is promoted by the Dutch National Institute for Public Health and Environment (RIVM) and accessible for the public at www.rivm.nl/cib/themas/teken-lyme. Calculations have indicated that a Lyme vaccine could be economically attractive when used in persons living in an area with an annual risk of more than 1% of contracting Lyme borreliosis.[128] Such regions are prevalent in North Eastern USA,[129] however are yet to be identified in the Netherlands. The only licensed Lyme vaccine was based on recombinant OspA, which showed a 70% efficacy in phase III human trial.[130] It became available in 1998, but was removed from the market in 2002 because of public perceptions on adverse events. We recently discussed the possibilities for vaccine strategies against Lyme borreliosis,[131] such as vaccines based on the combination of *Borrelia* and tick (saliva) proteins. Indeed, antibodies against the tick salivary gland protein Salp15 – by itself able to impair *B. burgdorferi* infection in tick-challenged mice – had synergistic effects in conjunction with a vaccine directed against *B. burgdorferi* antigens.[132] Also, combination vaccines, consisting of multiple *Borrelia* antigens, showed higher efficacy compared with vaccination based on single or double antigens, in mice.[133] Such novel approaches have yet to be tested in humans. Finally, to reduce the risk of human Lyme borreliosis, preventive approaches include decreasing tick densities, tick *B. burgdorferi* s.l. infection rates and wildlife control. The latter can be achieved by the use of acaricides.[134] However, resistance to acaricides in ticks occurs, and acaracides are harmful for humans, animals and the environment.[135] Novel strategies comprise wildlife Lyme vaccines[132] or prophylactic treatment of wildlife with doxycycline[136] (and personal communication Dr. Piesman, Center for Disease Control (CDC), Fort Collins, Colorado, USA).

CONCLUSIONS/SUMMARY

Lyme borreliosis is endemic in the Netherlands with a yearly incidence of EM of approximately 133 cases/100,000. It is a zoonotic disease, with well-defined symptoms, caused by *B. burgdorferi* s.l. and transmitted by ticks. Diagnosis of early Lyme borreliosis, i.e. EM, is made clinically and there is no need for serological tests. Diagnosis of later manifestations is based on the combination of specific clinical symptoms and positive serology and/or other diagnostic tests. In longer lasting manifestations of Lyme borreliosis sensitivity of serology approaches 100%. Specificity of serology is lower, since the seroprevalence of antibodies against *B. burgdorferi* s.l. is approximately 4 to 8% in the general population. This includes treated Lyme borreliosis patients, individuals who have spontaneously cleared asymptomatic *Borrelia* infection or have cross-reacting antibodies. Therefore, in individuals with aspecific symptoms it is not recommended to test for antibodies against *Borrelia*. Antibiotics are effective in all manifestations of Lyme borreliosis and prognosis is usually excellent. However, a minority of patients experience potentially severe, but aspecific symptoms after previous adequate treatment for Lyme borreliosis. In these individuals, additional antibiotics have no substantial beneficial effects compared with placebo.[67-70] A challenge for the future is to develop a test to detect, or rule out, persistent active *B. burgdorferi* s.l. infection. This could reassure individuals who experience aspecific symptoms after previous recommended therapy for Lyme borreliosis, prevent unnecessary treatment and pave the way for research on the true aetiologies of aspecific symptoms after recommended antibiotic treatment for Lyme borreliosis. Finally, preventing Lyme borreliosis, by the development of novel vaccination strategies or wildlife control, remains an important challenge for the future. Thus, bearing these developments in mind, we should definitely not allow ourselves to become tired of Lyme borreliosis.

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REVIEW

Strategies in screening for colon carcinoma

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ABSTRACT

Colorectal cancer is the second most common cancer in Europe and meets the criteria for population screening. Population screening should lead to a reduction in CRC-related mortality and incidence. Several options are available for CRC screening, which can be itemised as stool-based tests and structural exams. Stool-based tests include guaiac and immunochemical faecal occult blood tests and DNA-marker tests. Structural exams comprise endoscopic techniques (flexible sigmoidoscopy, colonoscopy and capsule endoscopy) and radiological exams (double contrast barium enema, CT colonography and MR colonography).

Each test has its own test performance characteristics and acceptability profile, which affect the participation and effectiveness of the associated screening programmes. Faecal occult blood tests (FOBT) and flexible sigmoidoscopy (FS) are the only methods with a demonstrated mortality reduction during a ten-year period (FOBT 16% and FS 31%) while flexible sigmoidoscopy is the only screening test with a demonstrated reduction in CRC incidence (23%). It is likely that other screening techniques such as colonoscopy and CT colonography will also be effective in the reduction of CRC-related mortality. DNA-marker tests, capsule endoscopy and MR colonography are possible options for the future.

Keywords: Colorectal cancer, mass screening, screening test

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Europe. Each year, more than 400,000 persons are diagnosed with CRC and more than half of them will die from the disease.[1] In the Netherlands, 12,117 persons were diagnosed with CRC and 4810 persons died from CRC in 2008.[2,3] The clinical and pathological stage at the time of diagnosis largely determines the prognosis of diagnosed patients.[4] The CRC mortality rate could be decreased by the early detection of cancer, whereas both the mortality rate and the incidence can be decreased by the timely detection and removal of adenomatous polyps, precursor lesions of CRC.[5] As clinical symptoms develop late in the course of the disease, early detection requires additional action.

One of the ways of achieving early detection and prevention is through the development of population screening programmes in asymptomatic individuals.[6-9] CRC screening meets the criteria for population screening as defined by Wilson and Jungner.[10] CRC is an important health problem; its precursor lesions are recognisable and early removal of these lesions has been shown to be beneficial.

Several CRC screening tests are available. Each test has its specific test characteristics, with particular advantages and disadvantages that determine its acceptability profile.

In general, screening tests can be classified into two categories: stool-based tests and structural exams. Stool-based tests can be subdivided into tests that detect blood (guaiac and immunochemical faecal occult blood tests) and tests that detect faecal DNA that is shed from CRC. Structural exams can be subdivided into endoscopic techniques (flexible sigmoidoscopy, colonoscopy and capsule endoscopy) and radiological exams (double contrast barium enema, computed tomography (CT) colonography and magnetic resonance (MR) colonography). In this review, we discuss test performance, participation rate and effectiveness of the available population screening tests for CRC.

SCREENING TESTS

Stool-based tests

Faecal occult blood tests (FOBT) are based on the principle of detecting blood in stool that may originate from a bleeding CRC or large adenoma. FOBT is frequently used as

screening test worldwide because it is simple to perform at home, is non-invasive and relatively cheap. However FOBTs are not designed to detect precursor lesions. Adenomas and even CRCs usually bleed intermittently and therefore repetitive testing is required. Two main classes of FOBTs are available: guiac-FOBT (gFOBT) and faecal immunochemical tests (iFOBT or FIT). gFOBT detect any blood in stool whereas FIT are more specific for human haemoglobin.

Guiac-faecal occult blood test (gFOBT)

gFOBT detects blood in stool through pseudoperoxidase activity of haeme or haemoglobin. Persons are invited to collect three samples of stool at home and send it back by mail. The result of the test is usually interpreted by a laboratory assistant. In case of a positive test result, follow-up colonoscopy is advised. The test itself is easy to perform at home and no serious complications can be expected. In contrast, follow-up colonoscopy can cause complications in FOBT-based screening programmes, such as perforation and bleeding (0.001 to 0.02%).[11]

Test performance

Sensitivity is affected by factors such as test interpretation variability among laboratory assistants, brand of the test, and number of stool samples collected. Sensitivity is increased by adding a drop of water to the test before processing (rehydration of the test). Dietary intake of red meat (detection of non-human haemoglobin) leads to false-positives and vitamin C intake to false-negatives through blockage of the peroxidise reaction. gFOBT sensitivity is limited and variable for CRC (reported numbers vary between 13 and 64%) and for advanced adenomas (11 to 41%). Specificity for CRC ranges from 91 to 95%.[11-13] In population screening, the non-rehydrated gFOBT resulted in a low test positivity rate (0.8 to 3.8%) and a positive predicted value (PPV) for CRC of 5.0 to 18.7%. Rehydrated gFOBT resulted in a higher test positivity rate (1.7 to 15.4 %) and a lower PPV (0.9 to 6.1%) than non-rehydrated gFOBT.[11]

Participation

To be effective, gFOBT-based screening programmes require annual or biannual testing. Therefore, participation in subsequent screening rounds is essential. Reported percentages of persons attending a first gFOBT screening round ranged from 53 to 67%. The percentages of persons attending all screening rounds were only between 38 to 60% while participation in at least one of the screening rounds was between 60 to 78%, in a programme with a minimal length of ten years.[11,14]

Effectiveness

gFOBT was the first screening test with a documented CRC-related mortality reduction during a ten-year period.[11,14] The estimated CRC-related mortality reduction ranged from 13 to 33% in four randomised controlled trials (RCTs), in which FOBT screening was compared with no screening. Combining the results of all eligible RCTs that used both annual and biannual screening leads to an estimated 16% RR reduction in CRC mortality in an intention-to-screen meta-analysis (RR 0.84; 95% confidence interval [CI] 0.78 to 0.90). In studies that only used biannual screening an estimated 15% CRC mortality reduction (RR 0.85; 95% CI 0.78 to 0.92) was achieved, from which can be concluded that biannual screening is sufficient.[11] A CRC incidence reduction was only observed in one RCT, but this effect could be largely attributed to the high colonoscopy and following polypectomy rate in that study. The other three (truly population-based) RCTs reported no significant CRC incidence reduction.

Immunochemical faecal occult blood test (FIT)

FIT detects human globin in stool via an immunochemical reaction and is generally considered a superior screening test compared with gFOBT. Whereas gFOBT only determines the presence or absence of blood in stool in absolute terms, FIT allows quantitative measurement of haemoglobin in stool. This allows fine-tuning of the cut-off level for referral for follow-up colonoscopy, aiming at an optimal balance between test performance and the available colonoscopy capacity in a certain country.[15,16] In contrast to gFOBT testing, no dietary restrictions are needed. Processing of the test is automated in a clinical laboratory and only one measurement is needed for FIT, versus three stool samples for gFOBT-based screening. As adverse events are also associated with follow-up colonoscopies rather than with stool testing itself, complication rates of FIT-based screening programmes will be comparable with that of gFOBT-based screening, provided the positivity rates are comparable.

Test performance

With FIT, high sensitivity can be achieved. Its sensitivity in detecting CRC (66 to 82%) and advanced adenomas (27 to 30%) is at least similar to that of gFOBT, without a reduction in CRC specificity (95 to 97%).[12,17] In persons who participated in screening, detection rates for advanced adenomas and cancer were higher with FIT compared with gFOBT (2.4% *vs* 1.1 to 1.2%) whereas the PPV for CRC seems equal (10 to 11% *vs* 8.6 to 9.7%).[18,19]

Participation

In two Dutch population-based screening studies, in which participants were randomised to receive either gFOBT or FIT, participation was higher in the FIT group (60 and 62%) than in the gFOBT group (47 and 50%).[18,19] However, participation in the gFOBT-screening arm in these trials was lower than in other European studies (53 to 67%). This

could be due to the current low awareness of CRC and CRC screening in the Netherlands.[20,21] However this could also imply an increase in participation for FIT-based screening in the future. The most important reason for the higher participation rates for FIT screening is presumably the easier performance of the test.[22]

Effectiveness

There is no evidence from RCTs that CRC-related mortality is reduced over a ten-year period of FIT screening. Because FIT-based screening has been shown to lead to higher participation and detection rates than gFOBT-based screening, it is likely that the associated effectiveness is at least comparable. In one RCT 94,000 persons were randomised to either one round of FIT testing and completion of a risk questionnaire or no screening.[23] No colon cancer mortality reduction was shown after a follow-up period of eight years: CRC mortality was 90 per 100,000 in the screening group *vs* 83 per 100,000 in the control group (p=0.222). There were some major limitations is this study: only one round of FIT was offered and flexible sigmoidoscopy instead of colonoscopy was performed in case of a positive test result.

DNA markers

A relative new method of CRC screening is based on DNA markers in stool (sDNA) and carries promise for screening in the future. A multipanel of DNA markers is needed because no single gene mutation is present in all cells shed by adenoma or cancer. A panel of DNA markers comprising selected point mutations on APC, KRAS and p53 genes plus long DNA (PreGen-Plus) is being tested in two large average-risk cohorts.[13] Another panel marker comprising methylated vimentin, mutant KRAS, and mutant APC (SDT-2) is being tested in a smaller study.[24] However, costs are high compared with FOBT.

Test performance

One study that used PreGen-Plus showed a limited CRC sensitivity (52%) and acceptable specificity (94%).[13] Another study using PreGen-Plus showed 20% sensitivity and 96% specificity for 'screen-relevant neoplasia' (curable-stage cancer, high-grade dysplasia, or adenomas > 1 cm). This study also reported a sensitivity of 40% for screen-relevant neoplasia using SDT-2.[24] The limited sensitivity can be explained by the use of a panel of DNA markers identifying the majority but not all CRC.

Participation

So far, no studies have been performed evaluating sDNA in an invitational population-based screening setting. It is not known to what extent individuals would be more willing to participate in CRC screening by sDNA than by gFOBT or FIT.

Effectiveness

No data are available evaluating reduction of CRC-related mortality by sDNA during a period of ten years.

ENDOSCOPIC TECHNIQUES

Flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) is an endoscopic procedure, in which the distal 40 to 60 cm of the colon is inspected by a regular forward viewing endoscope. Individuals will receive an enema 30 to 60 minutes before the examination for distal bowel cleansing. FS can be performed without sedation. In contrast to FOBT testing, small early neoplastic lesions in the distal colon are detected and these can directly be removed. If an adenoma of any size is detected in the distal colon a full colonoscopy is advised, because of the increased risk of advanced adenomas or cancer in the proximal colon.[25] Quality of the examination and thus of the screening programme might be difficult to assess since insertion depth is sometimes difficult to determine.[26] Furthermore, FS needs to be performed by trained endoscopists with acceptable adenoma detection rates.[26] Complications such as bleeding or perforation occur in FS screening, because of the screening method itself (0 to 0.03%) or due to follow-up colonoscopy (0.3 to 0.5%).[27-29]

Test performance

In a screening programme in which eligible patients were selected by general practitioners (GP), FS had a higher detection rate for advanced adenomas and cancer compared with FIT in one screening round (5.2 *vs* 1.2%, OR 0.22; 95% CI: 0.14 to 0.35%).[30] Isolated proximal advanced adenomas or cancer will be undetected in persons attending FS screening, because, in the absence of distal adenomas, they will not receive a follow-up colonoscopy. In persons attending colonoscopy screening, the percentage of asymptomatic individuals with isolated proximal advanced adenomas or cancer is estimated at 1.3 to 5%.[31,32]

Participation

Participation to once-only FS screening is lower than in once-only gFOBT or FIT screening.[19] However the large variance of participation rates to FS screening is remarkable in Europe. A Dutch trial reported a participation rate of 32% whereas large Norwegian and UK trials have reported participation rates of 64 and 71%.[19,27,28] The Norwegian and Dutch trials were truly invitational population-based whereas the UK trial used a two-step procedure in which people were only randomised after having shown an interest in being screened. Screening

programme participation could be lower over ten years because it is generally advised that repetitive five yearly testing is necessary in case of a negative test result.[33]

Effectiveness

Recently, Atkin *et al*. (UK trial) were the first to show evidence of mortality reduction in FS screening.[27] In contrast to FOBT screening, a CRC incidence reduction was also expected because of the removal of the precursor lesions in FS screening. After having shown an interest to be screened, asymptomatic individuals were randomised on a 2:1 basis resulting in a control group (113,195 persons) and an intervention group (57,237 persons). In the intervention group, 40,621 persons (71%) attended FS screening; advanced adenomas or cancer was detected in 5%. In all people offered a single round of FS screening, a 23% reduction of CRC incidence (HR 0.77; 95% CI 0.70 to 0.84) and a 31% reduction in CRC related mortality (HR 0.69; 95% CI 0.59 to 0.82) were observed. In persons who actually attended FS screening, the incidence and mortality reduction were higher: 33% (HR 0.67; 95% CI 0.60 to 0.76) and 43% (HR 0.57; 95% CI 0.45 to 0.72), respectively. A Norwegian group reported the results of an interim analysis of a population-based study (NORCCAP trial) for CRC incidence after a follow-up period of seven years and for CRC mortality after six years.[28] In contrast to the UK trial, no significant difference was found in CRC incidence between the screening and control group (134.5 *vs* 131.9 cases per 100,000 person-years). Nor was a significant difference observed in CRC-related mortality (HR 0.73; 95% CI 0.47 to 1.13). There was a significant CRC-related mortality reduction of 59% in persons who actually attended FS screening (HR 0.41; 95% CI 0.21 to 0.82). Hoff *et al*. mentioned two reasons for the limited effect of FS screening in this interim analysis: the screening test does not work or the development of CRC from precursor lesions will take longer than the follow-up time. The second possibility is more likely, considering the results of the UK trial.

Two other large RCTs of FS screening are currently ongoing. The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial included 154,942 men and women aged 55 to 74 years, who were randomised to either repeated FS or no screening.[34] In the Italian SCORE trial, 34,292 individuals were randomised to either once-only FS-based screening or no screening.[29]

Colonoscopy

Colonoscopy is an endoscopic technique that allows inspection of the entire colon. It is considered the reference standard for detection of colorectal neoplasia. Colonoscopy is an invasive and burdensome procedure and involves full bowel cleansing. The main advantage of colonoscopy is that removal of adenomas or early cancer can be performed during the same procedure whereas all other screening tests require colonoscopy for confirmation and removal. Another advantage is that histological assessment of resected polyps and irresectable lesions can be directly obtained, which is necessary to determine the surveillance interval or the need for further treatment. The risk of complications with colonoscopy is estimated between 0.1 and 0.3%; adverse events include postpolypectomy bleeding and perforation.[35,36]

Test performance

In an average risk cohort of persons 50 to 66 years of age who underwent full colonoscopy, advanced adenomas were detected in 5% and CRC in 0.9%.[36] Although colonoscopy is considered to be the reference standard for the detection of colonic neoplasia, polyps are still missed. A substantial adenoma miss rate of 20 to 26% for any adenoma and of 2.1% for large adenomas (≥10 mm) was reported in tandem colonoscopy studies.[37] Adenoma detection rate is highly dependent on quality standards including the colonoscopist and several patient-related factors.[38] Optimal bowel preparation, sufficient withdrawal time, complete examination of the colon and, to a lesser extent, optimal withdrawal technique, are associated with lower polyp miss rates.[39-42]

Participation

It is not known yet to what extent persons would participate in a truly invitational population-based colonoscopy screening programme. Colonoscopy is offered in Poland and Germany as part of an implemented programme.[36,43] In Germany, the average annual participation rate is about 2.6% of those entitled to screening colonoscopy: men and women aged 55 years or older.[44] The Italian study reported a lower participation rate for colonoscopy screening compared with FS and FIT screening: 27% *vs* 32 and 32%, respectively.[30] In this study, subjects were selected by GPs and randomised to one of the groups within GP. This study can not therefore be considered an invitational population-based screening study.

It would come as no surprise that participation rates in colonoscopy screening are lower than in FOBT or FS-based screening, because the procedure is simply more invasive and burdensome. Yet, as patients only have to participate once every ten years, achieving comparable programme adherence over a similarly long period could be challenging for FOBT and FS-based screening. Colonoscopy can be performed with long intervals as the risk of developing CRC after a negative colonoscopy remains low for more than ten years.[45,46]

At this moment, a large Spanish RCT is ongoing comparing the participation rate in biannual FIT screening to that of one-time colonoscopy screening, with a follow-up time of ten years.[47] A Dutch RCT (COCOS trial) is ongoing,

comparing participation in one-time colonoscopy screening to that in one-time CT-colonography screening.[48] This trial is conducted in the same setting as earlier RCTs in the Netherlands which investigated participation rates in gFOBT, FIT and FS based screening, allowing a comparison, be it an indirect one, of all of these screening tests.

Effectiveness

There are no empirical estimates of the effects of colonoscopy screening on CRC-related incidence and mortality. The Nordic-European Initiative on Colorectal Cancer (NordICC) trial is a multicentre collaborative effort in the Nordic countries, the Netherlands and Poland in which 66,000 individuals are randomised to either colonoscopy screening or no screening. A 15-year follow-up is planned and an interim analysis will be performed after ten years. Results are expected in 2026.[49] In the Spanish trial, CRC-related mortality is directly compared between biannual FIT and colonoscopy screening and results are expected in 2021.[47]

Capsule endoscopy

Colon capsule endoscopy is a new technique to visualise the colon, originating from small bowel imaging. Colon capsule is an ingestible capsule consisting of an endoscope equipped with a video camera at both ends. Van Gossum *et al*. were the first to evaluate the effectiveness in a prospective setting. In high-risk patients, the sensitivity and specificity in detecting polyps ≥6 mm was 64 and 84% respectively and in detecting advanced adenomas 73 and 79%.[50] The per-patient sensitivity and specificity with the second-generation capsules were promising, with an estimated sensitivity and specificity of 89 and 76% for polyps ≥6 mm, and 88 and 89% for polyps ≥10 mm.[51] Compared with full colonoscopy, the accuracy of capsules is considerably lower and an even more extensive bowel cleansing is needed. Capsule endoscopy has not yet been evaluated in an average risk screening population.

RADIOLOGICAL EXAMS

CT colonography

CT colonography (CTC), also called virtual colonoscopy, allows an examination of the entire colon. Interpretation is made possible in two-dimensional and three-dimensional images. A small rectal catheter is inserted into the coecum and carbon dioxide is needed for bowel insufflation. CTC is considered a less invasive colonic exam compared with colonoscopy.[52,53] The preparation is reduced to 150 ml of iodinated contrast agent for tagging combined with a low residue diet. This preparation is now indicated as best practice and can replace the extensive bowel preparation needed for colonoscopy.[54] If polyps or CRC are detected on CTC, a colonoscopy will follow for confirmation and, if possible, subsequent therapy. CTC screening leads to exposure of ionising radiation to asymptomatic persons. A low-dose protocol is regularly used and inherent chances of radiation-induced malignancy are low. Extra colonic structures are made visible on CTC. This could be beneficial, but the risks and costs associated with false-positives will be considerable. The risk of complications is extremely low, no perforations or other serious complications have been observed in a large CTC screening cohort.[55]

Test performance

A large screening trial evaluating CTC and same day colonoscopy studied 1233 asymptomatic individuals and reported high sensitivity (94%) and specificity (96%) per patient for large adenomas (≥10 mm) and these dropped for smaller lesions (≥6 mm): 89 and 80% respectively.[56] In another study, performed across 15 institutions and including 2500 asymptomatic individuals, sensitivity for adenomas ≥10 mm and cancer was 90%, specificity 86%, at a PPV of 23% and an NPV of 99%.[57] The diagnostic yield for detection of advanced neoplasia of CTC is comparable with that of colonoscopy: 3.2 *vs* 3.4%.[55]

Participation

So far, no data are available evaluating participation to an invitational population-based CTC screening programme. The ongoing Dutch COCOS trial compares participation in CTC-based screening to that in colonoscopy screening.

Effectiveness

The effectiveness of CTC screening on CRC incidence and mortality has not yet been demonstrated. To our knowledge, no RCTs are ongoing evaluating this effect.

MR colonography

Magnetic resonance imaging (MRI) of the colon has been increasingly studied in the last years. This imaging technique also allows examination of the entire colon. The lack of ionising radiation and high soft tissue contrast could favour MRI over CTC. As in CTC, the use of ionising contrast agent for tagging could be mandatory.[58]

Accuracy of MR colonography in detecting colorectal polyps was evaluated in both high-risk and normal-risk cohorts. In a meta-analysis, its sensitivity in the detection of CRC was estimated at 100%. For polyps with a size ≥10 mm, per-patient sensitivity and specificity estimates were 88 and 99%.[59] One study only included asymptomatic individuals with a normal risk for CRC. Sensitivity and specificity for polyps ≥10 mm were 70 and 100%.[60]

Double-contrast barium enema

Double contrast barium enema (DCBE) was the first radiological exam that could evaluate the entire colon. DCBE coats the mucosal surface with high-density barium. Multiple radiographs are made while constantly changing the patient's position. Full bowel preparation is needed and test performance is low: sensitivity for lesions ≥10 mm and ≥6 mm is only 48% and 35% respectively in a high-risk cohort.[61] The higher performances of CTC and MR colonography make DCBE-based screening studies illogical.

DISCUSSION

Of all available options for CRC screening, gFOBT and FS-based screening are the only strategies with a documented CRC-related mortality reduction during a ten-year period. gFOBT and FS-based screening can therefore considered to be effective.[11,27] Development in CRC screening is ongoing and it is very likely that other screening methods (iFOBT, CTC and colonoscopy) are effective as well. Stool marker tests, capsule endoscopy and MR colonography should not be used for CRC screening at this moment, but have potential for the future. DCBE is considered to be an inferior modality, now surpassed by CTC, and should not be used for screening. The characteristics of all screening tests are summarised in *table 1*.

FOBT is easy to perform at home and the associated costs are low. FOBT requires biannual testing and follow-up colonoscopy is needed in case of a positive test result. High participation rates during both first and subsequent screening rounds are essential for the effectiveness of the screening programme. Nowadays FIT-based screening is generally preferred over gFOBT-based screening, because of the better participation and detection rates. Its quantitative nature allows the definition of an optimal cut-off level aiming to match detection rates in a given population to colonoscopy capacity. However, definitive evidence of the effectiveness for FIT-based screening is lacking.

In contrast to FOBT, CRC-related incidence reduction was observed in FS-based screening. It is very likely that colonoscopy-based screening would also result in CRC-related incidence reduction. The success of FS-based and colonoscopy-based screening is dependent on the quality of the examination which should be carefully guaranteed if implemented. Colonoscopy is considered the best test to detect colorectal neoplasia, but polyps are missed by this modality as well. CTC can detect polyps with similar accuracy compared with colonoscopy and is therefore also a good candidate for CRC screening.

To implement a specific CRC screening programme, various factors should be taken into account. Besides factors as test accuracy and participation rates, programme adherence has already been proven necessary (biannual screening by FOBT). However high test accuracy is often associated with high burden and low programme adherence. Furthermore, high participation rates of a single round of screening would not automatically result in high programme adherence during a longer period. The results of the interim analysis of the NORCCAP study may illustrate that programme adherence for FS screening is as important as for FOBT screening. No significant CRC-related mortality reduction was shown after seven years of follow-up by a single round of (invitational population-based) screening. This might indicate that a second round after five years is actually needed.[28] It seems logical that a CRC-related mortality reduction will be shown in the future, because development to CRC will probably take longer than seven years. This is confirmed

Table 1. *Characteristics of all screening tests*

	gFOBT	FIT	FS	CTC	Colonoscopy
Sensitivity (%) for detecting cancer or advanced adenoma[62]	20	32	83	97	100
Detection rate for advanced adenoma and cancer (%) intention-to-treat[18,19,30,36,55]	1.1[19] to 1.2[18]	1.2[30] to 2.4[18,19]	5.2[30] to 8.0[19]	3.2[55]	3.4[55] to 5.9[36]
Participation rates (%) in the Netherlands[18,19,48]	47[18] to 50[19]	60[18] to 62[19]	32[19]	expected in 2011[48]	expected in 2011[48]
Complication rate (%) in population screening screening test only + colonoscopy	- 0.001-0.02	- 0.001-0.02	 0-0.03 0.3-0.5	expected in 2011[48] expected in 2011[48]	0.1-0.3 N/A
Significant reduction CRC incidence (%) intention-to-screen[11,27]	No[11]	No	23[27]	?	?
Significant reduction CRC mortality (%) intention-to-screen[11,27]	16[11]	?	31[27]	?	?

[62]colonoscopy is used as reference standard; [18,19]derived from population-based RCT; [30,36,55]derived from non-population invitational based screening programme; [11]CRC incidence reduction was not found by three of four RCTs included in meta-analysis

by the results of the UK trial, but this study used a two-step invitation strategy and can not be considered to be truly invitational population-based.[27]

In the US, persons can choose the screening test that they prefer. Two major US guidelines, from ACS-MSTF and USPSTF, both published in 2008, came to different recommendations on CRC screening while the literature supporting both guidelines was almost identical.[33,63] ACS-MSTF distinguishes between cancer *prevention* tests and cancer *detection* tests. The cancer prevention tests are mainly focussed on detection and removal of the premalignant lesions to prevent development of cancer while the cancer detection tests concentrate mainly on early detection of cancer. ACS-MSTF stipulated that the best test is the test that the patient will take, but recommends cancer prevention over cancer detection tests. In contrast, the USPSTF guidelines are based on a simulation decision model and require a higher level of evidence to include a test. The USPSTF recommend focusing on strategies that maximise the participation rate and therefore also includes cancer detection tests in their guidelines.

In most of the EU member states, the USPSTF approach is more supported than the ACS-MSTF one. The Council of the European Union (EU) has recently recommended screening by FOBT, but a population-based approach to programme implementation. Most of the EU member states have already adopted this approach.[64] Some of the member states (Germany, Austria) have established non-population-based screening programmes while some have implemented other strategies than FOBT. Poland began an opportunistic colonoscopy programme in the early 1990s and also other member states have adopted endoscopic methods (Austria, Germany, Greece), as a supplement to FOBT or an alternative screening method. Differences in programmes and strategies might make it difficult to evaluate and to compare the effect of screening in all of Europe.

In conclusion, strong evidence is available on the effectiveness of FOBT screening.[11] FOBT, and especially FIT, resulted in the highest participation rate in pilot programmes.[18,19] Most of the EU member states have now implemented or will implement a FOBT programme. However, other screening techniques (FS, colonoscopy, CTC, MR colonography or stool marker tests) could be implemented as a supplement in existing programmes or replace FOBT in the future.

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REVIEW

Type B lactic acidosis in solid malignancies

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ABSTRACT

Background: Type B lactic acidosis is thought to be a rare complication of malignancy. It was first described in patients with acute leukaemia by Field *et al.* in 1963. Since then, it has been observed more often, in particular in haematological malignancies and rarely in solid tumours.
Methods: Previously reported cases of lactic acidosis in solid malignancy are reviewed. In addition, we report a case of type B lactic acidosis in a woman with metastatic breast cancer. Afterwards, we speculate on the elusive pathophysiology of this oncological emergency.
Results: 14 cases of lactic acidosis due to solid malignancies, without prior chemotherapy, were identified. The cases were published from the year 1978 to 2006.
Discussion: Several theories concerning the mechanism for type B lactic acidosis in solid malignancy have been postulated. During the last decade, more and more evidence supports the role of overproduction of lactic acid due to ischaemia in the neoplastic tissue bed and with cancer cells having an aberrant energy production.

Keywords: Lactic acidosis, malignancy, solid tumour

INTRODUCTION

Lactate is a tricarbonic anion which can be viewed as a metabolic dead-end in that it is initially produced from pyruvate and later re-converted into pyruvate. The major factors determining lactate production are the pyruvate concentration and to a lesser extent the redox state of the cytosol. These in turn are influenced by glycolytic flux, the transamination from alkaline and mitochondrial function.[1] One molecule of lactate combines with one positive hydrogen ion to form lactic acid.[2] Normal subjects produce 15 to 20 mmol/kg of lactic acid per day. Virtually all tissues can produce lactic acid, the major contributors being skin, erythrocytes, brain and skeletal muscle.[3] In normal conditions, lactate is metabolised mainly in the liver and to a lesser extent in the kidneys to form glucose, a process known as gluconeogenesis. Furthermore, lactate utilisation is determined by the flow of pyruvate into the Krebs cycle.[1,2]

Hyperlactataemia and subsequent lactic acidosis develops in cases of increased production and/or diminished utilisation of lactate. It should be noted that hyperlactataemia is not necessarily accompanied by acidosis and can occur due to peripheral hypoxia, leading to dysfunction of the mitochondrial respiratory chain, causing a switch to anaerobic metabolism. This occurs in states such as sepsis, burns or trauma.[1] Current diagnostic criteria for lactic acidosis are a pH less than 7.35 and a plasma lactate concentration greater than 5 to 6 mmol/l.[1,4] Symptoms of lactic acidosis are variable and can include increased respiratory rate, tachycardia, abdominal pain, and hepatomegaly.[2]

There are several types of lactic acidosis. Those most commonly described and seen in clinical practice are type A and B. Type A lactic acidosis is due to tissue hypoperfusion or acute severe hypoxaemia. In type B lactic acidosis several mechanisms may be involved, such as toxin-induced impairment of cellular metabolism, or regional areas of ischaemia.[5] The aetiologies of type B lactic acidosis consist of hereditary metabolic diseases, drugs / toxins (for example biguanides, salicylates, nucleoside reverse transcriptase inhibitors,[6] and methanol) and systemic disorders. Underlying diseases associated with type B lactic acidosis are diabetes, thiamine deficiency, pheochromocytoma, sepsis, liver disorders and malignancy.[1,5]

Type B lactic acidosis is also thought to be a rare complication of malignancy. It was first described in patients with acute leukaemia by Field *et al.* in 1963.[7] Since then, it has been observed more often especially in haematological malignancies,[8] but has also been noticed in solid nonhaematological tumours such as small cell lung cancer, cholangiocarcinoma, breast cancer, gynaecological cancers and metastasis from unknown primary carcinoma.[9-15]

We have reviewed previously reported cases of lactic acidosis in solid malignancy. In addition, a new case of lactic acidosis in a patient with metastatic breast cancer is presented. Finally, we speculate on the elusive pathophysiology of this oncological emergency.[2]

METHODS

We searched MEDLINE and PubMed in English, Dutch and German language publications, with the search strategy: "lactic acidosis AND tumours" and "solid tumours AND acidosis". We also used the reference list of all reviews and relevant papers that we retrieved. We identified cases of lactic acidosis associated with solid malignancies that satisfied the criteria of Luft and associates[4] (pH ≤7.35 and plasma lactate concentration ≥5 mmol/l) and in which the malignancy was the primary cause of the lactic acidosis. Patients who had previously received chemotherapy or had another cause of lactic acidosis beside malignancy were excluded. In addition, we report one additional case not previously published.

RESULTS/REVIEWS OF CASES REPORTED IN THE LITERATURE

Fourteen cases of lactic acidosis due to solid malignancies (1978-2006) were identified, in patients not previously undergoing chemotherapy (*table 1*). Most of the cases were seen in the USA, but there were also single reports from hospitals in the UK, India and Japan.

CASE REPORT

An 86-year-old white female was sent to the emergency department of our hospital in August 2008 because of two weeks of fever, nausea, anorexia, non-productive cough and generalised malaise.

Her past medical history included a colon carcinoma cured after a hemicolectomy in 1981, type 2 diabetes mellitus, hypertension and two myocardial infarctions. She was currently taking glimepiride, atorvastatin and perindopril. She did not use metformin for her diabetes. She was a non-smoker and drank no alcohol.

On the day of admission, she had a normal mental status, was normotensive, had a pulse of 100 beats/min, a body temperature of 38 °C, a respiratory rate of 25/min, and was in mild respiratory distress.

On physical examination, she had nipple retraction with a firm, nontender mass in the right breast, abdominal tenderness on deep palpation and hepatomegaly.

Laboratory investigations showed a noticeable elevated lactic acid of 7.5 mmol/l. In addition, haematology and electrolytes were normal, plasma creatinine was 120 µmol/l. Liver enzymes were elevated but liver function tests appeared normal.

Arterial blood pH was 7.35, pCO_2 was 3.3 kPa, PO_2 was 12.5 kPa and bicarbonate (HCO_3) was 13 mmol/l. An increased anion gap of 26 mmol/l was calculated. Computed tomography of the thorax and abdomen showed diffuse liver metastasis and a mass in her right breast. Biopsies of the lesions revealed a high-grade infiltrating ductal adenocarcinoma of the breast and metastasis to the liver.

Furthermore, as our patient had a normal glucose level, no signs of intestinal ischaemia or tissue hypoxia, and was not taking any lactic acidosis-inducing drugs, we concluded the lactic acidosis was due to malignancy. Determination of thiamine and riboflavin revealed a mild vitamin B1 deficiency (69 nmol/l, reference value 100 to 200 nmol/l). Treatment was initiated with 100 mg per day of intravenous thiamine, but had no effect on her lactic acidosis. Sodium bicarbonate ($NaHCO_3$, 100 mmol/24 hour, intravenously) was administered to relieve symptoms, such as her 'Kussmaul' breathing. Lactate level remained 12 mmol/l.

Because of her age and suboptimal performance score only capecitabine monotherapy was started. Despite this treatment, the patient deteriorated and died a few weeks after discharge from our hospital.

Table 1. *Cases of lactic acidosis due to solid tumours, without previously given chemotherapy*

Tumour	# patients	Range age (years)	Liver metastasis	Survival after presentation	Range lactate mmol/l	pH	Reference
Small cell carcinoma lung	9	45-70	+ and -	5 days - 16 weeks	11.3-26.6	7.11-7.29	9-11,16-21
Large cell carcinoma lung	1	80	-	NA	13.1	NA	22
Endometrial carcinosarcoma	1	72	-	4 weeks	9.2	7.20	14
Cholangiocarcinoma	1	70	+	2 weeks	12.5	7.11	12
Breast adenocarcinoma	2	36-61	+	Unknown-remission	5.0-17.2	7.27- 7.31	13,23

NA = not analysed.

DISCUSSION

Type B lactic acidosis seems to be a well-recognised problem in patients with uncontrolled leukaemia. Reviewing the literature and reports of nonhaematological solid tumours, type B lactic acidosis seems more common then previously believed and may well be an under-recognised problem.

The aetiology of type B lactic acidosis in solid malignancy remains elusive. Studying the pathogenesis of type B lactic acidosis is difficult and looking into the behaviour of tumour cells one can see why. Solid tumours present with great cellular heterogeneity, and often consist of variable proportions of malignant cells, stromal regions, infiltrated defence cells, and necrotic areas. Furthermore, the tumour cells themselves exhibit variable biological properties with regard to proliferation, differentiation, metabolic activity and viability as a consequence of both genetic instability and of heterogeneous microenvironmental conditions.[24] Some of these characteristics may well contribute in the pathogenesis of type B lactic acidosis in malignancy.

Several theories concerning the mechanism for type B lactic acidosis in solid malignancy have been postulated. Hypotheses include liver dysfunction due to massive liver metastasis leading to lactate underutilisation and subsequently lactic acidosis. Indeed, most of the reported cases of solid tumours and lactic acidosis, including our case, were accompanied by extensive liver metastases.

It should be noted, however, that neoplasm-associated lactic acidosis has been reported without liver metastasis, and in most cases parameters of hepatic function (bilirubin, albumin and prothrombin time) were normal. Furthermore, lactic acidosis is uncommon in severe liver diseases such as hepatitis, cirrhosis and fulminant hepatic failure. Liver involvement alone cannot fully explain the syndrome, and its exact role is not completely understood.[1,2,25]

During the last decade more and more evidence has emerged supporting the role of overproduction of lactic acid due to ischaemia in the neoplastic tissue bed and cancer cells having an aberrant energy production.[1,26] It has been suggested that large tumours or tightly packed bone marrow may limit blood supply and oxygenation, leading to a hypoxic microenvironment and a subsequent production of lactic acid.[1,17] In sharp contrast to most normal tissues, it was shown by the German biochemist Otto Warburg in the early part of the 20th century that cancer cells frequently develop a modified glucose metabolism, whereby a significant portion of the blood glucose consumed by the tumour cells is converted one step beyond pyruvate, i.e., to lactic acid, even when oxygen is plentiful.[26] Nowadays numerous studies have demonstrated that the majority of tumour cells *in vivo* exhibit elevated levels of glucose transport and elevated rates of glycolysis that result in an increase in the production of lactate.[26] Although glucose is the major source of lactate in most solid tumours, glutamine and serine can also contribute to the formation of this tricarbonic anion.[24,27]

The last few years major discoveries concerning the high rate of glycolysis in cancer cells have been published.

Recently, hypoxia-inducible factor (HIF) was identified as an important factor in the upregulation of glycolytic enzymes. HIF activation not only stimulates glycolysis but also actively attenuates mitochondrial respiration, making HIF a key regulator of cancer cell metabolism.[28] HIF leads to overexpression or aberrant expression of mitochondrially bound glycolytic enzymes such as hexokinase. Hexokinase is the first rate-limiting enzyme in the glycolytic pathway. The high affinity of hexokinase for glucose can help cancer cells maintain a high rate of glycolysis in the presence of oxygen, allowing tumour cells to proliferate rapidly and survive for prolonged periods. Insulin regulates the activity of this enzyme; however, many cancer cells overexpress insulin-like growth factors and their receptors that can mimic many activities of insulin.

The activity of pyruvate dehydrogenase (PDH), which catalyses the rate-limiting reaction of converting pyruvate to acetyl-CoA, is primarily regulated by pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase phosphatase (PDP). In the glucose metabolic pathway, PDK inhibits the conversion of pyruvate to acetyl-CoA thus blocks the entry to Krebs cycle by phosphorylation and inactivation of PDH. Such action of PDK inhibits mitochondrial respiration and shifts the cellular biogenesis to cytoplasmic glycolysis.

As no single theory gives a universal explanation, experts believe the aetiology of type B lactic acidosis associated with (solid) malignancy is multifactorial.[1,25,29]

Consistent with the theory of overproduction are clinical data in which succesful treatment of the underlying malignancy resolved the lactic acidosis and recurrence of the neoplasm was associated with relapse of acidosis.[1,10,17,25,30-33]

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ORIGINAL ARTICLE

One-year epidemiology of fever at the Emergency Department

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ABSTRACT

Background: Although fever is recognised as a major presentation symptom at Emergency Departments (EDs) and is often used as a rationale for the institution of antibiotics, few studies describing patients with fever as the sole inclusion criterion at the ED of a general hospital have been performed. The objective of this study is to describe epidemiology of non-surgical febrile patients at the ED and to identify risk factors for adverse outcome.

Methods: Blood, sputum, urine and faeces cultures, urine sediments and throat swaps for viral diagnostics were obtained from febrile ED patients. Outcome parameters were bacterial/viral infection, non-bacterial/non-viral infection, non-infectious febrile disease; mortality, hospital admission, admission to the intensive care unit (ICU) and length of hospital stay.

Results: 213 Patients were included (87.8% were hospitalised, 8.5% were admitted to ICU, 4.2% died). In 75 patients (35.2%), bacterial infection was confirmed; in 78 patients (36.6%) bacterial infection was suspected. In nine patients (4.2%), viral diagnosis was confirmed; in six patients (2.8%), a viral condition was suspected. The most frequently encountered infection was bacterial pneumonia (58 patients, 27.2%). Only older age was correlated with mortality (ρ=0.176, p=0.01).

Conclusion: A majority of the febrile patients were admitted to the hospital, mostly for bacterial infection. An overall mortality rate of 4.2% was registered. Only a few risk factors for adverse outcome could be identified in this cohort. Overall, the outcome of patients presenting with fever at the ED is rather benign.

Keywords: Anti-bacterial agents; emergency service, hospital; fever; infection; prognosis

INTRODUCTION

Febrile illness is one of the most frequent causes of attendance at emergency departments (EDs) worldwide. Among the most frequently reported specific principal reasons for visiting an ED in the United States in 2005, fever was the third reported complaint, accounting for 4.4 to 7.5% of all ED consultations and up to 30% in non-surgical patients.[1,2] Although the underlying conditions causing the symptom of fever vary considerably, it requires a systematic approach regardless of the underlying condition, concentrating upon a primary division between bacterial infections and other conditions and subsequent risk stratification, often using the same parameters. Despite many efforts, including the implementation of faster and more accurate diagnostic tools, such as biomarkers, polymerase chain reactions (PCR) and radiological tests, the tests lack sufficient speed and reliability to justify clinical decision-making based on test results alone. Hence, both identification of bacterial infection and risk stratification remains very difficult in these patients in the emergency setting.[3-5] As a result, antibiotics are prescribed too frequently, leading to the worldwide problem of antibiotic resistance.

For an adequate risk stratification of febrile patients, a thorough knowledge about local epidemiology is required, and risk factors associated with adverse clinical outcome have to be identified. Moreover, as up to 50% of patients with fever may have a non-infectious aetiology,[6] better insight into the epidemiology of fever might also lead to a more restrictive use of antibiotics.

Although fever is recognised as a major presentation symptom at EDs and is often used as a rationale for the institution of antibiotics,[7] not many studies describing a cohort of patients with fever as the sole inclusion criterion

at the ED of a general hospital have been performed, especially not with the focus on non-surgical patients. Therefore, it remains unclear how many of these patients have been given antibiotics even though they did not actually suffer from a bacterial infection. Also, the epidemiology of patients with fever differs per region and changes over time,[8-12] which necessitates frequent epidemiological updates from different parts of the world. In addition, in many febrile cases the final diagnosis remains uncertain, due to sub-optimal supplementary diagnostics. A better insight into epidemiology may help to support or reject a diagnosis in these cases.

The purpose of this study was, first, to describe the epidemiology of non-surgical patients presenting with fever at the ED under optimal diagnostic conditions and, second, to identify risk factors for adverse outcome.

MATERIALS AND METHODS

Setting

ED of the Slotervaart Hospital, Amsterdam, the Netherlands, a general teaching hospital with a capacity of 410 beds with 70,000 new outpatients and 13,000 admissions yearly.

Design

Prospective cohort study of all adult, non-surgical patients presenting to the ED with fever (defined as tympanic temperature >38.2 °C), over a one-year period (January 2008 to January 2009). Non-surgical specialities included the departments of internal medicine, gastroenterology, cardiology, pulmonology, rheumatology, intensive care medicine and neurology.

Diagnostic procedures

To ensure an optimal diagnostic work-up of febrile patients, one year prior to the start of the study, a standardised protocol was introduced, allowing nurses in the ED to start taking blood, sputum, urine, wound or faeces cultures without having to wait for a doctor's order. According to this protocol, three blood cultures (aerobic/anaerobic) from three different venipuncture sites were obtained from every febrile patient. In case of respiratory symptoms, throat swaps for viral diagnostics were standardly performed (polymerase chain reaction (PCR) on *Influenza-A* and *-B, Parainfluenza-1-4, Adenovirus, Respiratory Syncytial virus (RSV), human Rhinovirus, human Metapneumovirus, human Coronavirus OC43, human Coronavirus 229E, human Coronavirus NL63, Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella* species), combined with bacterial sputum culture. In case of urinary symptoms, a urine sediment and culture were taken. In case of diarrhoea, faeces cultures were performed. Other diagnostic tests were ordered at the discretion of the attending physician.

To ensure an optimal inclusion, every working day, all ED patients of the day and night before were checked; if a patient had been missed, the responsible nurse was informed.

Definitions and outcome parameters

Final diagnoses at admission were retrieved from subsequent clinical records during one year of patient follow-up. The patients were confined to one of the following groups:

- confirmed bacterial infection: positive culture result in concordance with clinical findings;
- suspected bacterial infection: clinical findings strongly suggestive for bacterial infection, but without positive culture result; for instance, a patient with fever, purulent cough, crackles on auscultation and a lobar infiltrate on the thoracic X-ray;
- confirmed viral infection: positive viral PCR in concordance with clinical findings;
- suspected viral infection: clinical findings indicative of viral disease in the absence of positive bacterial cultures despite extensive culture taking and in the absence of underlying auto-immune or auto-inflammatory disease, malignancy, thrombo-embolic disease or medication use that could explain clinical findings;
- non-bacterial/non-viral infection: positive fungal culture or proven parasite in concordance with clinical findings;
- non-infectious disease: no evidence of infectious fever despite extensive supplementary diagnostics and a strong alternative diagnosis.

Outcome parameters were bacterial infection (confirmed or strongly suspected), viral infection (confirmed or strongly suspected), non-bacterial/non-viral infection, non-infectious febrile disease; mortality, hospital admission, admission to the intensive care unit (ICU) and length of hospital stay. Outcome parameters were correlated with patient characteristics, such as presence of diabetes mellitus, malignancy or immunocompromised state; sex, age and temperature at admission.

Statistics

Data are presented as numbers with percentages and medians with interquartile ranges (IQR; 25 to 75%). Correlations were analysed with Pearson's correlation test and are expressed as a Pearson's ρ with p values. A p value <0.05 was considered statistically significant. All statistical analyses were performed by using SPSS Statistics 17.0.0 (Chicago, ILL, USA)

RESULTS

Patients

Altogether, 213 non-surgical, febrile patients (111 female, 52.1%) were included during the study period, with a median age of 66 years. (IQR 46 to 79 years). Further patient characteristics are presented in *table 1*.

A total of 187 patients (87.8%) were hospitalised, nine patients (4.2%) died within a 30-day follow-up period (bacterial pneumonia (n=6); sepsis without definite focus (n=1); cellulitis (n=1); metastatic coloncarcinoma (n=1)) and 18 patients (8.5%) were admitted to the Intensive Care Unit (bacterial pneumonia (n=10, 4 died); urosepsis (n=5, none died); sepsis without definite focus (n=3, 1 died)). A majority of 171 patients (80.3%) were eventually diagnosed with a proven or strongly suspected infectious disease. In 75 patients (35.2%), a bacterial infection was confirmed and in 78 patients (36.6%) a bacterial infection was strongly suspected based upon clinical grounds. In nine patients (4.2%), a confirmed viral diagnosis was made whereas in six patients (2.8%) a viral condition was strongly suspected. Other patients were diagnosed with non-bacterial/non-viral infections (n=3, 1.4%; 2 malarial, 1 fungal infection) or a non-infectious febrile episode (n=9, 4.2%; 2 malignancy, 2 drug-induced fever, 2 autoimmune disease, 1 autoinflammatory disease, 1 cerebrovascular accident, 1 femur fracture). In 33 patients (13.6%), no definite diagnosis could be established.

Table 1. *Patient characteristics of patients (n=213), presenting with fever to the Emergency Department*

	n=213 **n (%) / median (IQR)**
Sex, female	111 (52.1)
Age, years	66 (46-79)
Diabetes mellitus	54 (25.4%)
Immunocompromised	33 (14.1%)
Malignancy	22 (10.3%)
Temperature, °C	38.9 (38.5-39.5)
Mean arterial pressure (MAP), mmHg	89 (74-103)
Heart rate, beats/min	103 (85-121)
Hospitalisation	187 (87.8%)
Duration of hospital stay, days	6 (4-11)
Admission to ICU	18 (8.5%)
Mortality	9 (4.2%)
Laboratory values at admission	
- Haemoglobin, mmol/l	8.1 (7.0-8.9)
- Leucocytes, giga/l	11.8 (8.4-15.5)
- Thrombocytes, giga/l	207 (153-263)
- C-reactive protein, mg/l	85.0 (36.3-175.1)
- Creatinine, μmol/l	94 (73.5-115.8)
- Albumin, g/l	33 (28-36)

Infections

The incidence of infections is shown in *table 2*. The most frequent infections were bacterial pneumonia (58 patients, 27.2%), urinary tract infections (45 patients, 21.1%), bacterial and/or viral upper respiratory tract infections (20 patients, 9.4%), skin infections (12 patients, 5.6%) and bacterial and/or viral gastroenteritis (8 patients, 3.8%).

Blood cultures were taken from 208 patients (97.7%); 52 were positive (24.3%) out of which 11 were probably contaminated. Of the blood cultures 41 (19.7%) were deemed truly positive. The most frequently encountered organisms were *S. pneumoniae* in pulmonary infections and *E. coli* in urinary tract infections. One Extended Spectrum β-Lactamase (ESBL) producing *E. coli* was cultured from the blood of a patient with urosepsis. No multi-resistant *S. aureus* (MRSA) were isolated.

Altogether, 151 additional cultures (urine, sputum, faeces, wound, liquor, throat, pleural fluid) were taken; 71 cultures (47.0%) were positive *(table 2)*.

Antibiotics

In 186 patients (87.8% of total) antibiotics were started. Amoxicillin/clavulanate was prescribed most frequently (26.9%), followed by ciprofloxacin (21.9%), ceftriaxon (12.0%), amoxicillin (9.0%) and metronidazole (7.0%). Double antibiotic regimens were administered in 48 patients, triple antibiotic regimens were administered in 11 patients. In the group of patients receiving antibiotics, 11 patients were later diagnosed as non-bacterial infection: viral diagnosis (n=6); non-bacterial/non-viral infection (n=2); no infection (n=3). Finally, 27 febrile patients did not receive antibiotics: non-infectious disease (n=8); no definite diagnosis (n=7); confirmed viral infection (n=1); suspected viral infection (n=5); suspected bacterial infection (n=5); confirmed bacterial infection (n=1). The one patient with a bacterial infection suffered from confirmed *C. jejuni* bacterial enteritis and made a full recovery with supportive therapy only. Immunocompromised state was strongly associated with the prescription of antibiotics (ρ 0.346, p<0.001). No significant correlation between prescription of antibiotics and comorbidity, such as diabetes mellitus or chronic pulmonary disease, could be observed.

Prognosis

Only older age was significantly correlated with mortality (ρ 0.176, p=0.01). No factors significantly correlated with ICU admission could be identified.

Factors correlating with hospital admission were older age (ρ 0.248, p<0.001), immunocompromised state (ρ 0.157, p=0.02) and the presence of a confirmed bacterial infection (ρ 0.155, p=0.04). Longer hospital stay was associated with female sex, older age and immunocompromised state (ρ 0.154, p=0.03; ρ 0.363, p<0.001; ρ 0.184, p=0.008, respectively), as were higher temperatures at

Table 2. *Incidence of febrile, non-surgical diseases, with most frequently confirmed pathogens in blood, urine, sputum, faeces and other sites at the Emergency Department*

Diagnosis	Blood	Urine	Sputum	Faeces	Other
Bacterial infections					
Pneumonia; n=58 (confirmed n=18; suspected n=40)	*S. pneumonia (8x)* *S. aureus (1x)* *E. coli (1x)*		*S. pneumonia (5x)* *K. pneumonia (2x)* *P. aeruginosa (1x)*		
Upper RTI; n=8 (confirmed n=3; suspected n=5)			*S. aureus (1x* *H. influenzae (1x)* *E. coli (1x)* *M. catarrhalis (1x)*		
UTI; n=45 (confirmed n=36; suspected n=9)	*E. coli (10x)* *P. mirabilis (3x)* *S. aureus (3x)* *E. faecalis (2x)* *K. pneumoniae (1x)*	*E. coli (16x)* *E. faecalis (5x)* *P. mirabilis (3x)* *P. aeruginosa (2x)* *K. pneumoniae (2x)* *S. aureus (2x)*			
Skin infection; n=3	*S. pyogenes (3x)*				
Cholangitis; n=3	*K. pneumoniae (2x)* *E. faecalis (1x)*				
Abscess; n=3	*E. coli (2x);* *Group C β-haemolytic streptococcus (1x)*				
Gastroenteritis; n=2				*C. jejuni (1x)* *C. difficile (1x)*	
Endocarditis; n=1	*S. constellatus*				
Diabetic foot; n=1	*S. aureus*				Wound culture: *S. aureus*
Tuberculosis; n=1					Pleural fluid culture: *M. tuberculosis*
Appendicitis; n=1	*E. coli*				
Viral infections					
Pneumonia; n=5					PCR on throat swap: *Influenza A- (2x); rhino- (1x); parainfluenza 1- (1x); respiratory syncytial virus (1x)*
Upper RTI; n=5 (confirmed n=3; suspected n=2)					PCR on throat swap: *respiratory syncytial - (2x); parainfluenza 1-virus (1x)*
Meningitis; n=1					PCR on liquor: *enterovirus (1x)*
Non-bacterial/ non-viral infections					
Malaria					Peripheral smear examination: *M. vivax (2x)*
Fungal infection		*C. albicans (1x)*			

UTI = urinary tract infection; RTI = respiratory tract infection; PCR = polymerase chain reaction.

presentation (ρ 0.143, p=0.04). Having diabetes mellitus or underlying malignancy at presentation was niether significantly associated with worse outcome in terms of mortality, admission to special care unit or length of hospital stay, nor with the presence of bacterial and other infections.

DISCUSSION

Although fever is a very common complaint on EDs worldwide, studies describing the epidemiology of fever are scarce, perhaps because it is considered a commonplace and non-specific finding. Another reason for this lack of information, however, might be the fact that for a proper diagnosis of fever, accurate and extensive diagnostics have to be performed, which may be less of a priority in a hectic and crowded ED. Therefore, we sought to investigate the epidemiology of fever at the ED of a Dutch teaching hospital under optimal diagnostic conditions. Moreover, with a thorough knowledge of the local epidemiology, we tried to identify risk factors for adverse outcome in a febrile population.

The very high percentage of blood cultures taken shows that the implementation of our diagnostic protocol resulted in more extensive diagnostics. In the only earlier study, investigating a febrile population at an ED, blood cultures were taken in less than two thirds of all non-hospitalised

patients.[13] The high amount of other cultures taken underlines the optimal diagnostic conditions, enabling us to give a substantiated description of epidemiology.

We show that almost nine out of ten febrile patients are admitted to the hospital, with an average duration of a week. An overall mortality rate of 4.2% was registered, much lower than mortality rates as mentioned in two other ED studies in tropical countries[5,14] and in a Spanish study focusing on community-acquired bacteraemia,[12] but slightly higher than in an Australian cohort.[13] In our study, one in 20 patients were diagnosed with a non-infectious aetiology of the fever, which is lower than expected based on ICU findings,[6] but exactly as high as seen previously by our group in an Afro-Caribbean febrile population at the ED in Curaçao, Netherlands Antilles (*Limper et al, submitted for publication)*.

Gram-negative bacteria were the most frequent cause of bactaeremia, as was reported in an earlier European study.[12] However, upper and lower respiratory tract infections were the most common diagnoses in our cohort, most of these caused by gram-positive pathogens. This suggests that systemic infection with gram-negative pathogens is more common than with gram-positive bacteria in our population, contrasting with findings in the United Stated and Australia, where gram-positive bacteria have been shown to be the predominant cause of sepsis.[10,11] One might speculate that a relative increase of infections with multi-resistant streptococci and staphylococci in these countries is causing the difference.[15,16]

Only a few risk factors for adverse outcome could be identified in this cohort. As could be expected, age was strongly correlated with hospitalisation, longer hospital stay and mortality. Older people were relatively more prone to bacterial infections as a cause of the fever. Although an immunocompromised state was associated with worse outcome, presence of diabetes mellitus or underlying malignancy did not result in higher mortality numbers or more ICU admissions. The lack of increase in mortality within these groups may be due to the small numbers of fatalities in the overall group. The absence of association between malignancy and ICU admission may be attributed to a selective admission policy to this ward.

A relatively low total of 213 febrile patients were identified during this one-year study. This low number is largely due to the inclusion criteria, defining fever as a tympanic temperature >38.2 °C as measured at the ED, thus excluding febrile patients who had taken acetaminophen prior to the ED visit. However, by excluding those patients with self-reported fever, a 'clean' cohort of febrile patients could be constructed, resulting in stronger conclusions.

In conclusion, we show that the implementation of a diagnostic protocol at the ED is feasible, resulting in a high percentage of confirmed diagnoses of febrile patients and enabling us to give an overview of the epidemiology of fever in this group. Overall, the outcome of patients presenting with fever at the ED in this hospital is rather benign, only few patients suffering an adverse outcome.

ACKNOWLEDGMENTS

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CASE REPORT

Tako Tsubo cardiomyopathy, presenting with cardiogenic shock in a 24-year-old patient with anorexia nervosa

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ABSTRACT

Tako Tsubo cardiomyopathy is a serious condition that is caused by heart failure due to inordinate stress. We here present a case of a young woman with this disorder in association with anorexia nervosa. We postulate a pathophysiological relationship and discuss the management of Tako Tsubo cardiomyopathy.

Keywords: Tako Tsubo cardiomyopathy, apical ballooning syndrome, stress-induced cardiomyopathy, anorexia nervosa, hypoglycaemia, takotsubo

INTRODUCTION

We describe a rare case of Tako Tsubo cardiomyopathy (TTC) in a young female with anorexia nervosa presenting with cardiogenic shock. This case illustrates that TTC can be a serious complication in young females with anorexia nervosa. TTC is characterised by acute left ventricular contractile dysfunction, following intense emotional or physical stress. Tako Tsubo usually affects postmenopausal women. Presentation often resembles acute myocardial infarction with chest pain, ST elevation and a rise in cardiac enzymes.[1-3] However, no coronary event is found. The syndrome accounts for about 1 to 2% of the cases presenting with suspected acute coronary syndrome.[1,4] The left ventricle (LV) typically shows apical and mid-ventricular akinesis or dyskinesis with hypercontractile basal segments, resulting in an apical ballooning pattern.[1,5-7] The syndrome, first described in Japan in 1991, was named Tako Tsubo after a round-bottomed narrow-necked Japanese pot used for octopus fishing.[8] TTC is also known as stress-induced cardiomyopathy, broken heart syndrome or transient left ventricular apical ballooning syndrome. Recently, the Mayo Clinic proposed criteria for TTC *(table 1)*.[1,5] Therapy for TTC is supportive, since TTC is a self-limiting disease. Prognosis is favourable with full recovery of LV function in almost all cases. However, acute symptoms can be severe, including cardiogenic shock, ventricular arrhythmias and death.[5,6,9]

CASE REPORT

A 24-year-old woman was admitted to the department of psychiatry for treatment of severe emaciation. Her history revealed anorexia nervosa since the age of 18, resulting in multiple admissions. On admission her weight was 25 kg. During her admission to the psychiatric ward she lost consciousness due to severe hypoglycaemia, and she was transferred to the medium care unit for treatment with glucose and thiamine. Electrolyte disturbances,

Table 1. *Proposed Mayo Clinic criteria for apical ballooning syndrome or Tako Tsubo cardiomyopathy*

1	Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement The regional wall motion abnormalities extend beyond a single epicardial vascular distribution A stressful trigger is often, but not always present
2	Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
3	New electrocardiographic abnormalities (either ST-segmental elevation and/or T-wave inversion) or modest elevation in cardiac troponin
4	Absence of: pheochromocytoma myocarditis

namely hypokaliaemia and hypocalcaemia, were corrected, without signs of refeeding. The electrocardiogram (ECG) showed new slightly negative T waves in V3-4, thought to be caused by electrolyte disturbances. The patient recovered and was returned to psychiatry. Next morning she suffered severe hypotension: 75/45 mmHg (115/75 on admission), heart rate was 96 beats/min. Her glucose was 2.1 mmol/l, so glucose was administered. There were no complaints of chest pain or dyspnoea. The ECG showed new ST-segment elevation in the inferior and anterior leads *(figure 1)*. She was immediately transferred to the coronary care unit. On arrival, the glucose was 6.0. Echocardiography revealed a contractile pattern typical for Tako Tsubo: apical ballooning with apical akinesia and basal hyperkinesia *(figure 2)*. Blood tests showed elevated cardiac enzymes: creatinine kinase (CK) 1428 U/l, CK-MB 98 µg/l, troponin T 0.10 µg/l. The patient was urgently transferred to a nearby tertiary centre for immediate cardiac catheterisation. The coronary angiogram showed normal coronary arteries. To treat the persisting cardiogenic shock an intra-aortic balloon pump (IABP) was inserted and treatment with inotropes, fluid resuscitation and low-molecular-weight heparin was initiated. Electrolyte disturbances were corrected. The echocardiogram showed a pattern, consistent with features of TTC.

Figure 1.

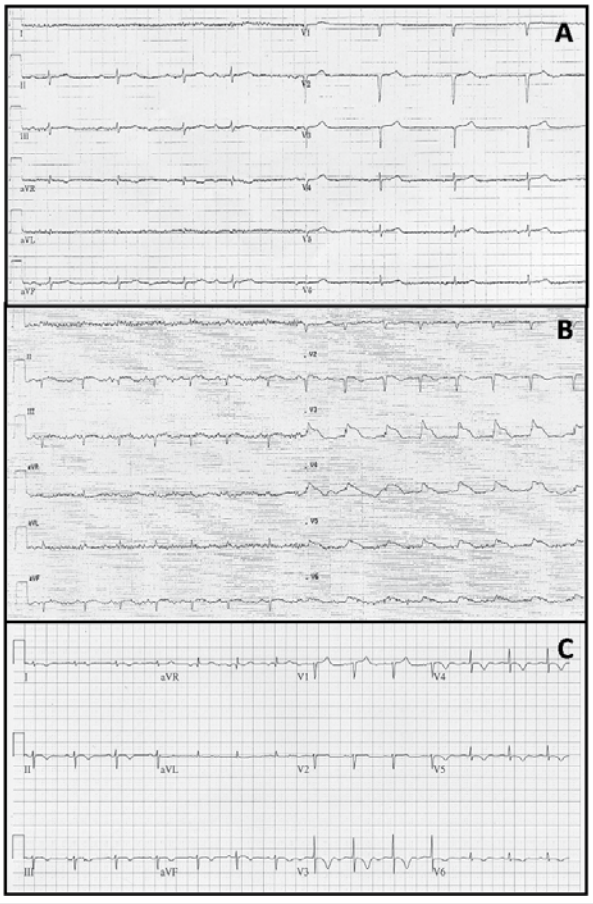
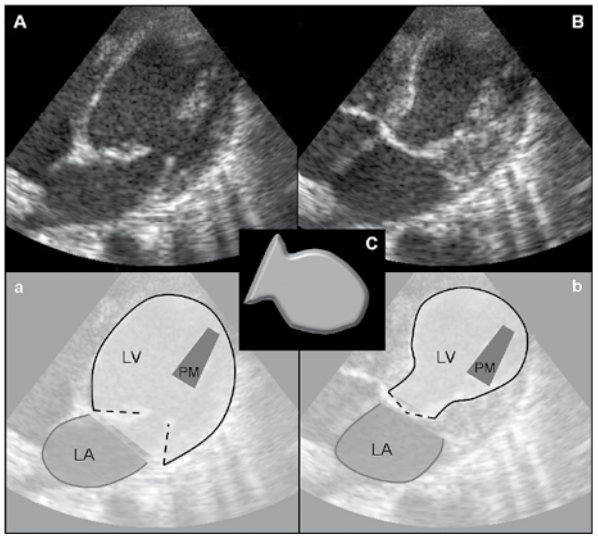


Figure 2.



Cardiac enzymes increased, topping at CK 5382 U/l and CK-MB 255 µg/l. Over the following days the ST elevation decreased. QT-interval prolongation and deep negative T waves emerged *(figure 1)*. After two days she was haemodynamically stable. IABP and inotropic support were withdrawn. Left ventricular function recovered substantially to an ejection fraction of 45 to 50% with mild wall motion abnormalities apicoanteroseptal over three months on ACE inhibitors.

DISCUSSION

In this report we present a case of a young female who suffered severe cardiogenic shock caused by Tako Tsubo cardiomyopathy, requiring intra-aortic balloon pump treatment. The rationale for reporting this case is the fact that it gives an opening to novel insights: it provides data that might increase our current understanding of TTC. The precise pathophysiology of TTC is unknown. The most favoured explanation is catecholamine-mediated myocardial stunning, as TTC is typically preceded by an emotional or physical stressor.[2,4,10,11] Commonly reported emotional stressors include death of a relative, severe argument or financial loss.[2,6,7,9] Among reported physical stressors are noncardiac surgery, asthma exacerbation, thyrotoxicosis and severe illness.[9,12] In our patient, the acute stressor appears to be hypoglycaemia, although refeeding and the mental stress of admission could also be stressors. It is known that hypoglycaemic stress increases plasma catecholamine

levels.[13] Therefore, hypoglycaemic stress may induce TTC. This case is unusual as TTC predominantly affects postmenopausal women (82 to 100% of cases).[5,6] Reduced oestrogen levels in postmenopausal women may alter endothelial function and microcirculatory vasomotor reactivity in response to catecholamine-mediated stimuli, possibly causing greater vulnerability to sympathetic-mediated myocardial stunning.[1,4,5,10] It may therefore be possible that the hormonal changes seen in young, severe anorectic patients sensitise them to TTC. To our knowledge only one report has been published on TTC in young females suffering from anorexia nervosa, describing three cases of possible TTC following hypoglycaemia.[14] All three cases showed ECG changes (either negative T waves or ST depression) and a rise in CK or CK-MB. Urgent echocardiography showed a Tako Tsubo pattern in only one case. In the other cases imaging was conducted only after five to seven days, showing no abnormalities. Cardiac catheterisation to exclude coronary occlusion was not performed in any of the cases. Therefore TTC was not proven, as in our case. As in the three cases mentioned above,[14] our case also suggests a relationship between TTC and anorexia-induced hypoglycaemia in young females. Further research is needed to reveal the pathophysiological mechanism of TTC and the relation with anorexia nervosa, oestrogen deficiency and hypoglycaemia. Treatment of TTC is mainly supportive. Besides ruling out acute myocardial infarction, management includes resolution of stress, monitoring and hydration.[1,4,5] Anticoagulation can be used to prevent left ventricular thrombosis. Beta-blockers are used empirically. Heart failure can be treated with diuretics and ACE inhibitors.[1,4,5] Cardiogenic shock due to pump failure is treated with inotropes and IABP. In case of cardiogenic shock left ventricular outflow tract obstruction must be excluded, because with this serious complication inotropes are contraindicated.[1,4,5] We believe that physicians treating anorectic patients need to be aware of TTC. We recommend routinely performing an ECG and echocardiogram to detect TTC in anorectic patients with chest pain, dyspnoea or hypotension. Concluding, Tako Tsubo cardiomyopathy can occur in young females with anorexia nervosa and hypoglycaemia might be a trigger. TTC has a favourable prognosis and LV function usually recovers fully. Despite its relatively benign nature in most cases, TCC can be characterised by severe clinical symptoms in the acute phase.

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CASE REPORT

Mastocytosis and diffuse large B-cell lymphoma, an unlikely combination

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ABSTRACT

Systemic mastocytosis may be accompanied by a second haematological malignancy, usually of myeloid origin. However, a number of case reports describe systemic mastocytosis coexisting with a second haematological malignancy of lymphoid origin. Here, we report a case of a 74-year-old man with systemic mastocytosis who developed a diffuse large B-cell lymphoma. A short overview of the literature concerning mastocytosis accompanied by a second haematological malignancy is presented.

Keywords: B-cell lymphoma, SM-AHNMD, systemic mastocytosis

INTRODUCTION

The term systemic mastocytosis (SM) encompasses a group of disorders defined by the accumulation and abnormal growth of mast cells. The physiological role of mast cells is mainly in type I immune responses. Clinical findings in SM are categorised into 1) constitutional symptoms, 2) skin manifestations, 3) mediator-related systemic events, and 4) musculoskeletal complaints.

Systemic mastocytosis is defined by the World Health Organisation according to major and minor criteria, which are explained in *table 1*.[1] SM is further divided into: indolent systemic mastocytosis (ISM) in which maculopapular skin lesions are usually present, aggressive systemic mastocytosis (ASM) defined by pathological mast cells infiltrating bone marrow, liver, spleen, gastrointestinal tract and the skeletal system, and mast cell leukaemia (MCL), characterised by pathological mast cells in high percentages (>20%) in bone marrow and peripheral blood, resulting in multi-organ failure and a fatal outcome.

Another subgroup is SM with an associated clonal haematological non-mast cell lineage disease (SM-AHNMD), in which the nature of the associated haematological dictates treatment and prognosis. Most often a myeloid neoplasm is diagnosed but lymphoproliferative neoplasms have also been described. In this case report, we describe a patient with systemic mastocytosis who developed a diffuse large B-cell lymphoma.

CASE REPORT

A 74-year-old male patient who had suffered from urticaria pigmentosa for years presented at our outpatient clinic with a history of attacks of bilateral abdominal pain and some weight loss during the past three months. His medical history was significant for biopsy proven urticaria pigmentosa for six years. He was taking levocetirizine on occasions. On physical examination he had skin lesions in accordance with urticaria pigmentosa. The spleen could not be palpated and there was no lymphadenopathy. A computed tomography (CT) scan of the neck, thorax and abdomen confirmed splenomegaly (16.2 x 5.6 cm) which was previously seen during ultrasound examination of the abdomen, and some borderline lymphomas. A 24-hour collection of urine showed elevated metabolites of histamine, the N-methylhistamine was 298 µmol/mol creatinine (<150) and the N-methyl-imidazole acetic acid 4.6 mmol/mol creatinine (0.90 to 1.9). Serum tryptase was 74.5 µg/l (reference values <11.4 g/l). The combination of biopsy proven urticaria pigmentosa, elevated histamine excretion and serum tryptase levels and splenomegaly led to the diagnosis of systemic mastocytosis, although a bone marrow biopsy was needed to meet the WHO criteria (*table 1*). A bone marrow biopsy was initially not performed, because his systemic complaints resolved spontaneously. No treatment was initiated at that time.

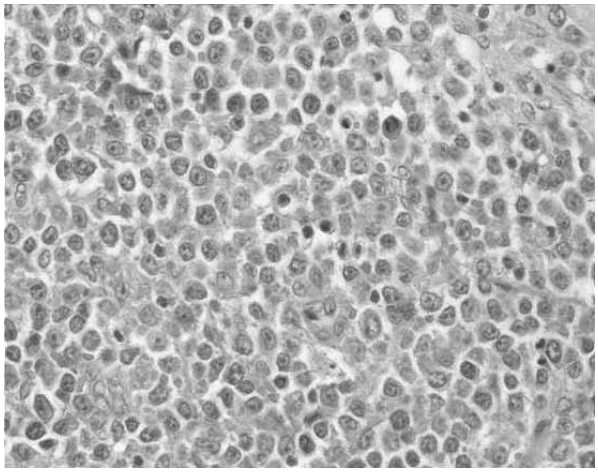
Table 1. *WHO classification of systemic mastocytosis (from WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Swerdlow et al. 2008[11])*

The diagnosis systemic mastocytosis can be made when the major criterion and one minor criterion or at least three minor criteria are present.

Major criterion:
Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).

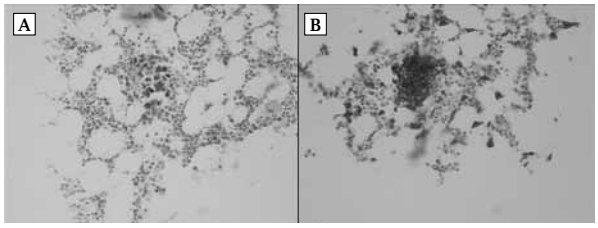
Minor criteria:
1. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical.
2. Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood or another extracutaneous organ.
3. Mast cells in bone marrow, blood or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.
4. Serum total tryptase persistently exceeds 20 ng/ml (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).

Figure 1. *Lymph node resection*



H&E staining. Histopathology of diffuse large B-cell lymphoma occuring in the lymph node. A diffuse lymphocytic infiltrate with blasts replaces the normal architecture.

Figure 2. *Bone marrow biopsy*



Abnormal amounts of both solitary and clustered mastocytes in the bone marrow. The typical metochromatic granules in mastocytes are stained in purple in the Toluidine blue stain (a). Immunohistochemistry shows mastocytes immunoreactive for CD 117 (b).

Seven months later, he was admitted to our department with a history of progressive lower back pain, radiating towards the groin. On physical examination, axillar lymphadenopathy was found. On the MRI scan of the vertebrae, there was a decreased T2-weighted signal on multiple levels. A new CT scan of the neck, thorax and abdomen showed widespread enlarged lymph nodes, mostly in the right axilla, alongside the aorta and the left iliac artery. Microscopic evaluation of a resected axillary lymph node showed blasts positive on CD20, CD79a and PAX5 staining, consistent with a diffuse large B-cell lymphoma (*figure 1*). CD117/KIT staining was negative. No mastocytosis was found in this lymph node. Bone marrow biopsy showed aggregates of spindle-shaped mast cells with reduced granulation, fitting the diagnosis systemic mastocytosis (*figure 2*). These cells were positive on CD117/KIT staining and negative on CD20, CD23 and PAX5 staining. A malignant lymphoma could not be found in this specimen. Based on these results stage III diffuse large B-cell lymphoma (DLBCL) coexisting with systemic mastocytosis was diagnosed (SM-AHNMD).

A treatment regimen of rituximab, cyclophosphamide, doxorubicin and prednisolone was started. Vincristine was not added because of his vulnerable clinical condition. The patient developed an allergic reaction to rituximab, which resolved after cessation of this therapy. Shortly hereafter, the patient developed leucopenic fever accompanied by a rise in lactate dehydrogenase up to 356 U/l after an initial drop in response to chemotherapy. He subsequently developed a persistent ileus and pneumonia. Further treatment was refused and shortly thereafter he died, probably due to progressive disease. Consent for post-mortem was not obtained.

DISCUSSION

It is well known that some patients with systemic mastocytosis develop a second haematological malignancy, called systemic mastocytosis associated clonal haematological non-mast cell lineage disease (SM-AHNMD).[1,2] SM-AHNMD encompasses systemic mastocytosis coexisting with myeloid as well as lymphoid malignancies, although the vast majority of these malignancies are of myeloid origin. Of the lymphoid malignancies occurring as SM-AHNMD, mostly B-cell malignancies are reported.[3,4]

A few cases of lymphoid neoplasms coexisting with systemic mastocytosis have been published. Sanz *et al.* presented a patient with systemic mastocytosis who developed chronic lymphocytic leukaemia (CLL).[5] Horny *et al.* described a case of a synchronous manifestation of systemic mastocytosis and CLL, in which a distinct clonal origin could be demonstrated by detecting an activating c-kit point mutation in mast cells from the bone marrow biopsy and wild-type c-kit in the microdissected

CD23-positive B lymphocytes.[6] Kim *et al.* described a patient with systemic mastocytosis coexisting with low-grade B-cell non-Hodgkin's lymphoma. Distinct clonal origins of the neoplastic mast cells and lymphoma cells were also demonstrated by presence of an activating c-kit mutation in the microdissected mast cells with absence of this mutation in the neoplastic B lymphocytes.[7] Focal accumulation of lymphocytes surrounding infiltrates of mast cells in patients with systemic mastocytosis is usually reactive, but it should be differentiated from clonal lymphoid disorders.

In our case, a distinct clonal origin of the neoplastic mast cells and lymphocytes could not be confirmed without post-mortem. However, immunohistochemical investigations clearly defined two distinct haematological conditions on two different anatomical sites, fitting the classification SM-AHNMD.[8] Due to the low prevalence, this combination of SM and diffuse large B-cell lymphoma can be accidental.[9] However, as mentioned in the article by Sperr *et al.,* in cases of lymphoproliferative malignancies mostly B cell malignancies may develop in SM.[10] This case is therefore important to report in addition to previous cases and as a learning point to always take into account the possibility of development of a second malignancy in a patient with SM.

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Schipper, et al. Mastocytosis and diffuse large B-Cell lymphoma.

Netherlands
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PHOTO QUIZ

Unusual mammary abscess

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CASE REPORT

A 70-year-woman, with a history of type 2 diabetes, presented at the emergency room with nausea, vomiting, diarrhoea and fever. Her primary care physician had been treating her with flucloxacillin because of an abscess of the left breast. This treatment did not result in improvement of her medical condition. Two months earlier she had reported discomfort in the right upper quadrant of her abdomen.

On physical examination she was an ill-looking woman, with a pulse rate of 88 beats/min, temperature of 34.7°C and blood pressure of 100/60 mmHg. Bowel sounds were normal and the abdomen was not tender on palpation. Examination of the breasts revealed a fluctuating mass in the left breast.

Laboratory results showed elevation of C-reactive protein (268 mg/l; upper normal limit (UNL) is 10 U/l) and leucocytes (24.5 x 10^9/l, UNL 11 x 10^9/l). Gamma glutamyl transpeptidase (301 U/l, UNL 40 U/l), alkaline phosphatase (171 U/l, UNL 120 U/l) and both aspirate aminotransferase (80 U/l; UNL 30 U/l) and alanine aminotransferase (146 U/l; UNL 35 U/l) were elevated as well. Bilirubin levels were normal. The urine sample revealed no abnormalities. Plain radiography showed no abnormalities of the chest. With a working diagnosis of sepsis, computed tomography was performed (*figures 1* and *2*).

Figure 1.

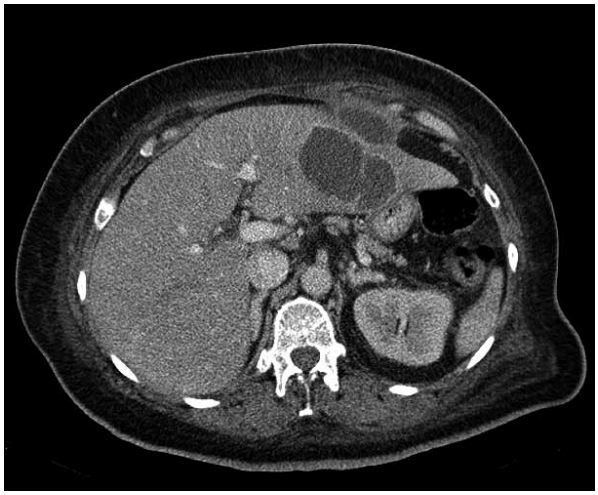
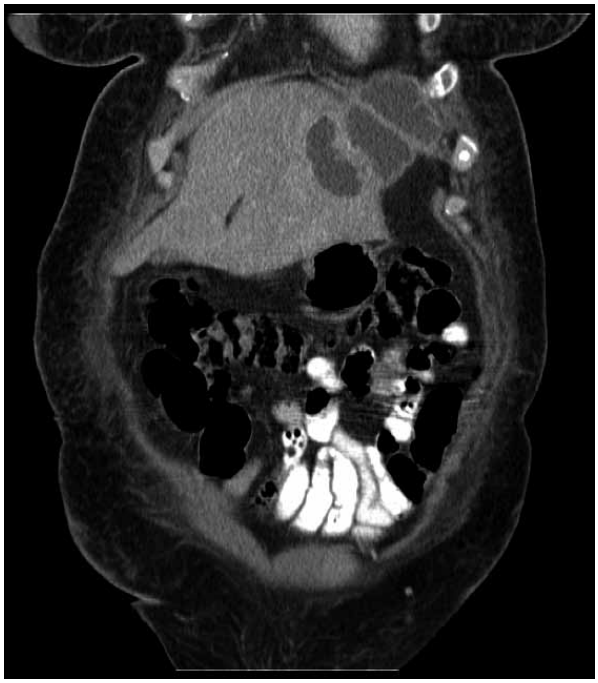


Figure 2.



WHAT IS YOUR DIAGNOSIS?

See page 138 for the answer to this photo quiz.

Netherlands
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PHOTO QUIZ

A 77-year-old female with macroglossia

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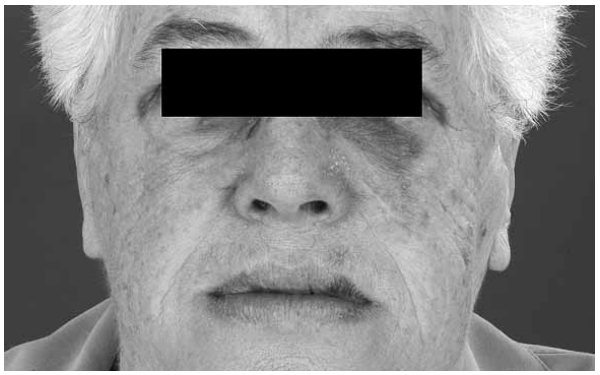
CASE REPORT

A 77-year-old woman was referred to the outpatient clinic because of a slowly progressive swelling of her neck and tongue in the last two years, causing difficulty with eating and speaking. She had never experienced respiratory problems. Her feet and hands were not enlarged. Furthermore, she had noticed spontaneous haematomas around her eyes and corners of her mouth which she blamed on her use of aspirin. Additionally, she complained of a numb feeling in digit V of her left hand. Physical examination indeed revealed macroglossia *(figure 1)*, swelling of the mouth floor and haematomas around both eyes and mouth *(figure 2)*. Hypesthesia of digit IV and V of her left hand was confirmed. Laboratory investigations showed an elevated erythrocyte sedimentation rate (25 mm/h) and total protein (95 g/l), normal blood count, a creatinine of 63 µmol/l, no proteinuria, normal calcium and normal liver enzymes. Thyroid-stimulating hormone and insulin-like growth factor 1 were 2.00 U/l and 10 nmol/l, respectively (normal).

Figure 1.

Figure 2.



WHAT IS YOUR DIAGNOSIS?

See page 140 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

Testicular mass in a geriatric patient

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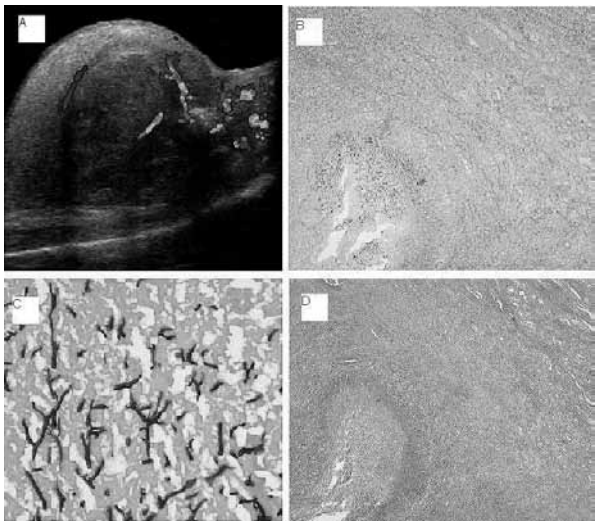
CASE REPORT

An 80-year old man was admitted suffering from a painful, enlarged right testicle for approximately one month. His medical history revealed a transurethral resection of the prostate for benign hyperplasia seven years before. The resection, performed in another hospital, was complicated by recurrent strictures of the urethra and several episodes of lower urinary tract infection. Internal urethrotomies and a holmium laser incision were used to resolve the strictures without lasting success. The patient did not have diabetes nor was he receiving any immunosuppressants. On presentation, genital examination revealed an indurated, tender, and enlarged right testicle. The patient was afebrile. White blood cell count was 7.9 x 10^9 /l (71% neutrophils), C-reactive protein was 3.6 mg/dl (normal limit <0.5 mg/dl), and alphafetoprotein was 11.6 ng/ml (normal limit <7.0 ng/ml). Other routine laboratory tests, lymphocyte subsets, and nitroblue-tetrazolium test were within normal limits. HIV serology was negative. A scrotal ultrasound revealed a testicular mass of approximately 3 cm which was cystic in the centre and more solid in character at the periphery. The Doppler signal showed a halo of intense hyperaemic flow with absent flow centrally *(figure 1A)*. Since a malignancy was suspected, a radical orchiectomy was performed. Pathological examination showed a soft cystic nodule in the testicle extending towards the epididymis and spermatic cord. Histological examination revealed a well-demarcated nodule characterised by a thick fibrous capsule, infiltrated by lymphocytes and plasma cells, and surrounding a collection of granulation tissue, and necrotic debris. A Grocotts's methenamine silver staining was performed which showed hyphae *(figure 1B-D)*.

Figure 1.



A. Scrotal Doppler ultrasound revealing a testicle containing a mass with a diameter of approximately 3 cm in the upper pole. The mass is hypoechoic and cystic in the centre and more solid in character at the periphery. The Doppler signal shows a halo of intense hyperaemic flow with absent flow centrally.

B-C. Grocott's methenamine silver stain showing hyphae.

D. Histological examination revealing a well-demarcated nodule characterised by a thick fibrous capsule, infiltrated by lymphocytes and plasma cells, and surrounding a collection of granulation tissue, fungal hyphae, and necrotic debris.

WHAT IS YOUR DIAGNOSIS?

See page 139 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 135)

UNUSUAL MAMMARY ABSCESS

DIAGNOSIS

Computed tomography with administration of contrast material showed a hypoattenuating mass in the liver that appeared to extend through the diaphragm into the left breast. These findings were consistent with a pyogenic hepatic abcess with a cutaneous fistula. Blood cultures and cultures of a specimen obtained by fine-needle aspiration of the liver lesion were positive for *Streptococcus anginosus*. The patient underwent drainage and was started on intravenous penicillin for a duration of four weeks. On colonoscopy there was no evidence of malignancy as a place of entry for the pathogen of the *Streptococcus milleri* group. On follow-up two months after drainage and antibiotic treatment, the patient was asymptomatic and had no recurrence of the abscess.

The commonest cause of liver abscess worldwide is amoebiasis, but in developed countries pyogenic causes are of increasing importance. In the developed world liver abscesses are the most common type of visceral abscess, with a mortality rate of 2 to 12%. Risk factors include diabetes, underlying hepatobiliary or pancreatic disease, and liver transplant. Independent risk factors for mortality include need for open surgical drainage, the presence of malignancy and the presence of anaerobic infection.[1] Infection in any site drained by the portal vein can cause portal pyaemia, with haematogenous seeding from the systemic circulation. Most commonly these abscesses involve the right lobe of the liver. Another important route is direct spread of infection from the biliary tree. Trauma and hepatic malignancy are uncommon causes.[2] Many pathogens have been described, reflecting the different causes, types of medical intervention and geographic differences. Polymicrobial infections are identified in about one-third of cases. The *Streptococcus milleri* or *S. anginosus* group (including *S. constellatus* and *S. intermedius*) is an important cause of liver abscess that should be followed by a search for simultaneous metastatic infections at other locations. Classical clinical manifestations of pyogenic liver abscess are upper abdominal pain and fever. Other common symptoms include nausea, vomiting, anorexia, weight loss, and malaise. For single abscesses with a diameter of less than 5 cm, either percutaneous catheter drainage or needle aspiration is acceptable. For percutaneous management of single abscesses with a diameter of more than 5 cm, catheter drainage is preferred over needle aspiration. Open surgical drainage is used when the abscesses are difficult to approach.[3] Antibiotic treatment needs to be continued for at least six weeks, depending on the extent of infection and the patient's clinical response. Patients who have had a good response to initial drainage should be treated with two to four weeks of parenteral therapy, while patients with incomplete drainage should receive four to six weeks of parenteral therapy. A cutaneous fistula is a rare complication of a liver abscess.[4]

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ANSWER TO PHOTO QUIZ (PAGE 137)
TESTICULAR MASS IN A GERIATRIC PATIENT

The silver stain shows dichotomically branching hyphae at 45° angles, which is typical for *Aspergillus* spp.[1] This leads to the diagnosis of urogenital aspergillosis, which was confirmed by a positive culture of *Aspergillus fumigatus*. No other foci were found by chest X-ray, computed tomography of the abdomen, and positron emission tomography.

While aspergillosis of the sino-pulmonary tract is a relatively common finding, *Aspergillus* infections of the urogenital tract are very rare. Only two cases of isolated testicle involvement have been described: Singer *et al.* reported a case in a renal transplant recipient receiving immunosuppressive agents, and another case was described in an HIV patient by Hood *et al.*[2,3] Our patient, although elderly, seemed immunocompetent; he did not have neutropenia or lymphopenia, and had not received corticosteroid treatment.

The most common route for developing aspergillosis is by inhalation of aerosols containing spores and subsequent haematogenous seeding.[1] Another transmission route is perioperative inoculation with development of postoperative invasive aspergillosis.[4] Similarly, the *Aspergillus* spores in our case probably entered the urinary tract during one of the multiple instrumentations of the urethra and inoculated the testicle by urinary reflux.

We decided to treat the patient with voriconazole, because histologically, the area of inflammation extended beyond the resection plane and the urine culture grew *A. fumigatus* postoperatively. These findings suggested that resection could be insufficient to clear the infection. Oral therapy was continued for four months. The optimal duration of therapy is unknown.[4] Seven months after cessation of therapy, there was no clinical recurrence.

ACKNOWLEDGEMENTS

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ANSWER TO PHOTO QUIZ (PAGE 136)

A 77-YEAR-OLD FEMALE WITH MACROGLOSSIA

The combination of macroglossia, spontaneous haematomas around the eyes and mouth, neuropathy and elevated total protein are suggestive of amyloidosis. Additional laboratory investigation revealed paraprotein, IgG kappa (30.2 g/l), with a total IgG of 33.7 g/l and decreased IgA (0.37 g/l) and IgM (0.17 g/l). Paraprotein (free light chain kappa, 728 mg/l) was also found in the urine. Bone marrow biopsy showed 30% monoclonal plasma cells (IgG kappa). With X-ray, two osteolytic lesions were found in the skull and left femur, respectively. A tongue biopsy stained with Conge red was negative, but a lip biopsy demonstrated focal amyloid. Cardiac ultrasound was normal.

Under the diagnosis of AL amyloidosis accompanying multiple myeloma stage IIIa, she was treated with thalidomide, dexamethasone and clodronic acid. Treatment was complicated by an allergic reaction to thalidomide and medication was switched to melphalan and dexamethasone. Over time, the paraprotein IgG kappa decreased to 2.0 g/l and IgA and IgM normalised. Although her macroglossia did not disappear, her tongue did not enlarge further. She has now been stable for four years.

AL amyloidosis is a rare plasma cell disorder with overproduction of monoclonal immunoglobulin light chains with deposition of amyloid fibrils in various organs. The symptoms depend mainly on the localisation of depositions. Macroglossia is virtually pathognomonic of systemic AL amyloidosis and is present in 10 to 23% of patients.[1] The degree of macroglossia can vary from slight tongue thickening to massive enlargement and interference with eating, swallowing, speaking, and breathing.[2] Amyloid deposits can infiltrate capillaries leading to weakening of microvascular tensile strength. In combination with factor X deficiency this is thought to be responsible for the haematomas. Factor X deficiency below 50% is present in less than 10% of patients with AL amyloidosis and presumably results from absorption of factor X by amyloid fibrils.[3] Amyloid deposition in the nervous system can cause peripheral neuropathy and can progress from a distal sensory deficit to a motor neuropathy in advanced cases. Kidney involvement, cardiac amyloid deposition and hepatomegaly are common but absent in this case.

In only a minority of patients is the AL amyloidosis related to multiple myeloma. The prognosis of this is poor with a median survival of four years. In conclusion, macroglossia without other symptoms can be the first indication of AL amyloidosis in multiple myeloma.

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Netherlands
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SPECIAL REPORT

Epidemiology of chronic pain and its treatment in the Netherlands

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ABSTRACT

Background: Chronic pain is common; however, good epidemiological data are scarce. Such information can help all the involved stakeholders to make responsible decisions about health budgets and prioritisation. This study aims to provide best-evidence epidemiological information about chronic pain in the Netherlands.

Methods: We performed a systematic search which yielded 16,619 references, 119 Dutch studies were relevant. We selected at least three studies per question that provided the most recent, representative and valid data.

Results: The prevalence of moderate to severe general chronic pain among Dutch adults was estimated at 18%. This prevalence was 27% and 55% for any cancer pain. Up to 74% of patients with general or non-cancer chronic pain get treated; this percentage is little higher for patients with cancer pain. A substantial proportion of the patients receive drug treatment for their pain, mainly NSAIDs, but also non-pharmacological interventions for pain are being used. Up to 43% of the chronic non-cancer pain patients report not receiving treatment and up to 79% of the patients believe their pain is inadequately treated. All studies reported a detrimental effect of chronic pain on quality of life, activities of daily living and mental health. Chronic pain is also associated with direct and indirect medical costs, and patients may have decreased income and additional out-of pocket expenses.

Conclusion: Chronic pain occurs frequently, has a negative impact on the patient and society and treatment may not always be adequate. Chronic pain should be seen as an important public health problem deserving more attention of Dutch healthcare workers and policy makers.

Keywords: Chronic pain, epidemiology, prevalence, treatment, the Netherlands

INTRODUCTION

Estimates of the prevalence of chronic pain vary widely and typically range between 10 and 30% of the adult population, although prevalence rates ranging from 2 to 55% have been reported.[1-3] This wide variation may reflect true differences between populations, but also the use of different definitions and classifications of chronic pain in epidemiological studies, for example duration of more than three or more than six months, and differences in assessment methods.[2] Chronic pain is often reported to be more common among women and in older age groups.[1,3] Subsequent to the variability in the definition of chronic pain, accurate data concerning prevalence, incidence, severity, treatment and utilisation of healthcare are scarce. National statistics in Europe do not tend to focus on chronic pain as a discrete entity, but rather see pain as part of other underlying diseases, a symptom. Additionally, many studies of chronic pain prevalence have been based in particular care settings, such as pain clinics, or in particular subgroups with certain underlying diseases. However, such data only represent subgroups of patients with chronic pain and do not provide insight into the general burden of chronic pain. Information about the epidemiology of chronic pain may dictate decisions of policy makers on the burden of the problem, health budget and prioritisation. Compared with cardiovascular disease, oncology, diabetes and mental

health, there often seems to be limited appreciation by decision-makers about the importance of chronic pain.

This study aims to provide information on the epidemiology of chronic pain, including cancer pain in the Netherlands. Information is based on reviewing published and unpublished literature, using the principles of systematic reviews. Specifically, this study provides best evidence on the prevalence and incidence of chronic pain, the treatment(s) given to patients with chronic pain and the impact of chronic pain in the Netherlands.

This study is part of a bigger effort which aims to provide information about the epidemiology of chronic pain in Europe. In the first step the research is performed in the separate countries. This is the first report in a series, which gives data from the Netherlands. Reports of other countries will follow. In a second step an overall analysis will be performed.

MATERIAL AND METHODS

We undertook a literature review on the most recent epidemiological data on chronic pain, separating cancer pain and non-cancer pain where possible. For this purpose, we formulated 21 research questions such as: 'What is the prevalence of chronic pain in the Netherlands?', 'What is the incidence of chronic pain in the Netherlands?', 'How many patients with chronic pain are treated in the Netherlands?', etc. In this paper we will focus on the questions on prevalence, incidence, treatment and impact of chronic pain.

Search strategy

We aimed to identify all relevant studies regardless of publication status (published, unpublished, in press, and in progress), or language.

In August 2009, we searched the following databases from 1995 onwards: MEDLINE, EMBASE, CDSR (Cochrane Library issue 2 2009), CENTRAL (Cochrane Library issue 2 2009), DARE (August 2009, CRD website), HTA (August 2009, CRD website), Guidelines International Network database (GIN website). The search strategies were developed specifically for each database

Furthermore, references in retrieved articles and systematic reviews were checked. Supplementary searches were undertaken as appropriate. Relevant websites were searched for national statistics, insurance data, health surveys and other relevant data.

Selection of studies

Two reviewers independently inspected the title and abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria were be applied. Any disagreement was resolved through discussion. Justification for excluding studies from the review (after having retrieved potentially relevant articles) was documented.

Included studies were categorised in order to get a list of relevant studies per question. Where there were more than three studies addressing a single aspect of any question, for each question the most relevant studies were extracted using the following criteria: representativeness (populations representative of the general target population preferred), size (large preferred), date of study (most recent preferred) and quality (higher quality preferred). Studies were ranked by these criteria and the three or four highest ranking studies were extracted.

Inclusion criteria

We included primary studies (epidemiological, qualitative, cost analyses etc.) or systematic reviews of primary studies published from 1995 onwards. Only relevant primary data used in any systematic reviews identified and fulfilling the inclusion criteria were used in the data analysis. Studies had to examine patients with chronic cancer or non-cancer pain from the Netherlands. Chronic was defined as pain of at least three months or having a chronic disease associated with pain such as osteoarthritis, fibromyalgia, rheumatoid arthritis or cancer. Excluded were studies on children and adolescents, patients with headache / migraine, patients with angina pectoris, pain associated with very specific medical conditions, such as Parkinson's disease and multiple sclerosis.

Assessment of methodological quality

Quality assessment was carried out by one reviewer and checked by a second, using the checklist as outlined in *table 1*. This checklist was developed for this review and was based on standard tools for reporting of studies. For observational studies the items were based on the STROBE statement.[4] Studies were rated 'high quality' if at least 7 criteria were met (6 if not a longitudinal study), 'medium' if 5 or 6 criteria were met and 'low' if fewer criteria were met (i.e. ≥4 No's or Unclear). Any disagreements were resolved by consensus. The results of the quality assessment have been used for descriptive purposes to provide an evaluation of the overall quality of the included studies. Based on the findings of the quality assessment, recommendations have been made for the conduct of future studies.

Data extraction

For each study, data were extracted by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus. We employed a narrative method to present the data. Such a synthesis involves the use of narrative text and tables to summarise data in order to allow the reader to consider outcomes in the light

Table 1. *Quality criteria used for the assessment of the observational studies. Criteria were to be answered with 'yes', 'no' or 'unclear'*

Criteria	Explanation: criterion is adequate if
Adequate description of study design and setting	Authors reported study design, setting and period of study
Adequate description of eligibility criteria (incl. description of diagnostic criteria for chronic pain condition)	Authors reported inclusion/exclusion criteria with diagnostic criteria to confirm diagnosis or confirmation that the doctors' patients had chronic pain
Study population is representative of target population (sample size, sample selection, demographics)	Authors described how the sample size was arrived at and how the patients were selected and the demographics of the sample should be described as comparable to the target population. For surveys, an attempt should be made to compare non-responders to responders
Adequate description of outcomes (and how / how often measured), exposures, predictors	Authors describe how they measure the outcome and clear definitions are given for key terms
Adequate description of statistical methods (incl. description of potential confounders and effect modifiers and how they were dealt with)	Authors describe their statistical methods and describe potential confounders or effect modifiers and how they were dealt with
Adequate description of study participants	Authors provide more than just age and gender (pain duration, occupations, pain type, etc.)
Adequate description of losses to follow-up (for longitudinal studies), loss to follow-up less than 10% at 12 months or less than 25% for longer follow-up	Authors clearly describe the losses to follow-up or if the loss is <10% by 12 months and <25% for periods longer than 12 months. NA for cross-sectional studies
Results reported as unadjusted and confounder-adjusted including precision	Authors report their results as unadjusted or confounder adjusted (or equivalent language – univariate, multivariate) and they provide precision (e.g. standard errors, standard deviations or confidence intervals). Authors should also indicate what confounders were adjusted for and why they were included.

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of differences in study designs and potential sources of bias for each of the studies being reviewed. Study characteristics and quality and results are presented in tables subdivided by questions.

In this review many different pain populations were examined. For clarity, the following terminology was employed: 'any chronic pain' included those with mild pain; 'general chronic pain' included those with cancer related pain.

RESULTS

The search yielded 16,619 references. Of these, 119 reporting on chronic pain in the Netherlands were included in this review. We selected at least three studies per question that provided the most recent, representative and valid data on data with respect to prevalence/incidence/treatment or impact. *Tables 2 and 3* present basic characteristics and methodological quality of studies that were included in this paper.

PREVALENCE AND INCIDENCE OF CHRONIC PAIN CONDITIONS

The Dutch adult population was approximately 12.5 million people in 2009.[5] The prevalence of moderate to severe general chronic pain among Dutch adults was estimated at 18%.[3] The overall prevalence of unexplained severe general chronic pain has been described as 7.91 per 1000 enlisted patients in general practice.[6] The prevalence of any general chronic musculoskeletal pain is estimated at 44.4%.[7] This pain was most frequently located in the lower back (prevalence 21.2%) and in the shoulders (15.1%) and neck (14.3%). The prevalence of chronic widespread pain (in upper and lower extremities, in back or neck and in left and right side of the body) was 5.2%.[7]

In a group of patients with cancer, 55% reported to have pain and 44% reported moderate to severe pain ((VAS ≥4).[8] The prevalence of pain in cancer patients receiving palliative care during the last three months of life (n=238) was 65%.[9] *Figure 1* presents the prevalence of specific chronic pain conditions.

Only four studies reported on the incidence of chronic pain and all reported incidence of specific disorders related to chronic pain. The overall incidence rate of any neuropathic pain, including non-chronic pain, was described as 8.2 per 1000 person years (95% CI 8.0 to 8.4).[10] Mono-neuropathy and carpal tunnel syndrome were the most common types of neuropathic pain. The overall incidence rate of Complex Regional Pain Syndrome (CRPS) was calculated at 26.2 per 100,000 person-years (95% CI 23.0 to 29.7).[11] The incidence of CRPS was more than threefold higher in females than in males (RR 3.4, 95% CI 2.9 to 3.9). The incidence varied profoundly with age, the highest incident rate was observed in the group aged 61 to 70 years. The incidence of occupational disability (after 52 weeks of sick leave) as a result of back disorders was 2.02 and 2.14 per 1000 workers per year for men and women, respectively.[12] The incidence rate of persistent pain three months after herpes zoster diagnosis was reported in the medical records of 2.6% (95% CI 1.7 to 4.0).[13]

Table 2. *Basic characteristics of included studies*

Name of first author, publication date	Study design	Study method	Type of chronic pain	Sample size	Demographics (including pain severity)
Alonso et al. 2004[30]	Cross-sectional study	Self-administered questionnaires	Any arthritis pain Arthritis (defined as 'arthritis or a type of rheumatic disease'). The duration of pain was not reported.	Total study population 24,936 Netherlands n=4059	Mean age 43.4 (SD 17.9) 46.1% males Pain severity not reported
Boonen et al. 2005[23]	Cost-of-illness study	Patients completed a cost diary for the duration of the study.	Any FM, any CLBP and any AS	FM: n=69 CLBP: n=110 AS: n=111	FM: Mean age 44.9 (SD 9.4), 13% males CLBP: Mean age 40.9 (SD 8.7), 40% males AS: Mean age 47.8 (SD 10.1), 71% males Pain severity not reported
Borghouts et al. 1999[17]	Descriptive retrospective study	GPs provided information on procedures and patients completed a self-administered questionnaire covering a 12-month period	Any chronic neck pain	Eligible: n=517, assessed: 487 (253 responders – data from GPs and patients, 234 non-responders – data from GPs only)	Median age 51 (IQR 41-60), 60% females Mean pain severity for subgroup of responders 4.9 (SD 2.4) using an 11 point ordinal scale where 0 = no pain and 10 = unbearable pain
Borghouts et al. 1999[24]	Cost-of-illness study	Study is based on prevalent cases of neck pain. Direct and indirect medical costs were estimated using national registries, reports of research institutes and healthcare authorities	Any neck pain	Not reported	Not reported
Borgsteede et al. 2007[9]	Cross-sectional study	GPs received a post-mortem questionnaire for each patient who died during the survey year. Information was also retrieved from electronic records.	Any chronic cancer pain in palliative patients	n=238	Not reported
Breivik et al. 2006[3]/Pain in Europe 2003[31]	Cross-sectional study	Telephone survey in two parts. First, persons were screened for chronic pain. Of those with moderate to severe general chronic pain, 300 were interviewed in-depth.	Moderate to severe general chronic pain long-lasting pain for ≥6 months; pain in last month; pain ≥2 times/week; and rating pain intensity ≥5 on 10-point NRS	n=3197 screened and n=300 interviewed	Mean age 51.3 years; 60% female 18% reported severe chronic pain (8-10 on NRS) 82% reported moderate chronic pain (5-7 on NRS)
De Mos 2007[11]	Retrospective cohort study	A search conducted in the IPCI database – a longitudinal general practice research database	Any complex regional pain syndrome	Database contains records of >600,000 patients from more than 150 GPs	Population is representative of the Dutch population regarding age and sex.
Demyttenaere et al. 2007[21]	Cross-sectional study	Face-to-face survey	Any chronic back or neck pain (not defined)	Netherlands sample n=1094	Mean age 45.0 years; 50.9% female Pain severity not reported
De Wit et al. 1999[15]	Prospective cohort study (carried out as part of larger RCT)	Patient interviews, medical and nursing records	Any chronic cancer pain Pain duration at least 1 month	383 were eligible (70 declined to participate because study was too burdensome (68.6%), lack of motivation (21.4%) or being too ill (10%) 313 participated	Mean age 55.5 years (SD 12.4); 62.6% females
Dieleman et al. 2008[10]	Cohort study	Study conducted in the IPCI database – a longitudinal general practice research database containing data of more than 500,000 patients records	Any general neuropathic pain (including chronic and non-chronic pain)	362,693 persons (1,116,215 person years)	Age and gender distribution similar to Dutch population Pain severity not reported

Table 2 to be continued on page 145

Continued

Table 2. *Basic characteristics of included studies*

Name of first author, publication date	Study design	Study method	Type of chronic pain	Sample size	Demographics (including pain severity)
Enting et al. 2007[16]	Cross-sectional study	Self-administered questionnaires and interviews. Incomplete questionnaires were followed up by phone.	Any cancer pain	n=915 completed questionnaire, and n=246 had pain (27%)	Patients with pain: Females 60% Mean age not reported Mean pain intensities on a 0-10 scale: Present pain: 3.8 (SD 2.4) Worst pain: 6.4 (SD 2.4) Average pain: 4.1 (SD 2.2)
Huisstede et al. 2008[22] DMC_3 study (national health survey of musculoskeletal conditions)	Cross-sectional study	Postal questionnaires	Any chronic complaints of the arm, shoulder and/or neck Pain at baseline and lasting more than 3 months in the last 12 months	n=3664 n=996 with any chronic pain of the arm, shoulder and/or neck	Of those with pain: 25–44 years 26% 45–64 years 45% 65+ years 29% Female 63% Pain intensity: 5.4% had continuous severe pain and 12.7% recurrent severe pain
Kemler and Furnée, 2002[25]	Cross-sectional study	Patient completed a 7-day diary	Any chronic refractory complex regional pain syndrome (CRPS)	n=50	Mean age (SD)=39 (11) years 30% males, 70% females All had a mean pain intensity ≥5 (on a 10-p VAS)
Kerssens et al. 2002[6]	Cross-sectional study	Data were collected from the Dutch Sentinel Practice Network. GPs included patients based on the study's inclusion criteria and researchers searched the database using relevant codes from classifications regarding pain syndromes or pain medication.	Severe unexplained chronic pain Pain which had lasted at least 6 months.	n=586	Mean age not reported; 71% females
Lame et al. 2005[19]	Cross-sectional study	Patients completed mailed questionnaires	Any non-cancer chronic pain Locations: neck pain and/or brachialgia (23.3%); back pain and/or sciatica (27.9%); other pain, such as complex regional pain syndrome type I and II, neuropathic pain syndrome, trigeminus neuralgia, FM and RA (15.7%); multiple pain localisations (30.1%).	n=1208	Mean 49.9 years (SD 14.7) female 62% Pain severity not reported
Opstelten et al. 2005[13]	Cross-sectional study	A search conducted in the 'Huisartsen Netwerk Utrecht' database, a general practice research database over a 5-year period.	Any post herpetic neuralgia. Any pain that persisted at least 1 month after herpes zoster diagnosis.	n=837	58% female; mean age not reported
Picavet and Hoeymans 2004[20] DMC_3 study (National health survey of musculoskeletal conditions)	Cross-sectional study	Postal questionnaires	Any OA knee or hip, any osteoporosis, any RA, any other chronic arthritis and any FM	n=3664	Demographics and pain severity not reported
Picavet and Schouten 2003[7] (National health survey of musculoskeletal conditions)	Cross-sectional study	Postal questionnaires	Any general musculoskeletal pain Pain lasting ≥3 months. Cancer pain not excluded (4% had tumour pain)	n= 3664	50.9% females; Age: 47% 25-44 yrs, 34.6% 45-64 yrs, 18.4% 65+ yrs

Table 2. *Basic characteristics of included studies*

Name of first author, publication date	Study design	Study method	Type of chronic pain	Sample size	Demographics (including pain severity)
Rupp et al. 2006[32]	Cohort study	Self-administered postal questionnaire and twice a short clinical assessment	Any RA	Baseline n=882, follow up: n=529	Mean age 59.8 (SD 14.8) Female 71.9% Pain severity VAS 0–100 mm mean 40.6 (SD 28.1)
Smalbrugge et al. 2007[33] Amsterdam Groningen Elderly Depression (AGED) study	Cohort study	Two face to face interviews and chart review (for recognition of pain)	Any general pain in the elderly (included non-chronic pain)	n=350 at baseline 229 at follow up	Mean age 79.3; SD 8.3; female 68.9% At baseline 27.5% serious pain symptoms ('unbearable pain' or 'constant pain') and 40.5% mild pain symptoms (reported positive on other items but had no 'unbearable pain' and no 'constant pain') At follow up 58.6% 'unbearable pain' and 66.0% 'constant pain' still present at 6 m.
Steenstra et al. 2006[12]	Cross-sectional study	Descriptive study using statistics from the National Institute of Social Insurance between 1980-1985 and 1999-2000	Any chronic back pain in persons who claimed occupational disability due to back disorders. Persons can claim this after 52 weeks of sick-leave	In 1999-2000, the number of insured persons was 6,710,551	57% males; mean age not reported
Van den Beuken-Van Everdingen et al. 2007[8]	Cohort study	At the outpatient clinics, the treating physician filled out the medical data. The day after, each patient was sent the self-report questionnaire.	Any cancer pain (assumed chronic) 26% had breast cancer, 15% had gastrointestinal cancer, 14% had prostate cancer and 10% had lung cancer	n=1383 55% had cancer pain	Overall sample: 52% females; Age: 4% between 20-40, 33% between 40-60, 56% between 60-80 and 7% 80+ years
Van Herk et al. 2009[18]	Cross-sectional study	A standardised pain questionnaire and data from medical charts	Any general pain in nursing home residents (72% had pain ≥3 months)	n=233	Median age 79 years (IQR 73-84); 70% were female Median pain : 5 on a 11 point numerical rating scale (NRS where 0 = no pain and 10 = worst possible pain) (IQR 2-7), 88 reported moderate or severe pain (>= 4 on NRS)
Van Tulder et al. 1998[14]	Cohort study	GPs provided information on diagnosis and treatments. Patients completed questionnaires at baseline and during follow-up.	Any chronic low back pain (current symptoms for ≥3 months)	524 patients (368 participants – data from GPs and patients, 156 non-participants -data from GPs)	Mean age: 41.1 years (SD 10), 51% men Pain severity: mean (SD) 10-p scale at baseline 5.6 (2.9) median (IQR) NHP pain subscale at baseline 40.5 (10.5-69.8)

N = number; SD = standard deviation; GP = general practitioner; ICPC = International Classification of Primary Care; IQR = inter quartile range; NHP = Nottingham Health Profile; FM = fibromyalgia; CLBP = chronic low back pain; AS = ankylosing spondylitis; RA = rheumatoid arthritis; OA = osteoarthritis; NRS = Numerical Rating Scale; IASP = International Association for the Study of Pain; RCT = randomised controlled trial; CRPS = chronic refractory complex regional pain syndrome; VAS = visual analogue scale; ICD = International Classification of Diseases.

TREATMENT OF PATIENTS WITH CHRONIC PAIN

How many get treated

Of patients with general or non-cancer chronic pain, 57%[3] to 74%[14] get treated and this percentage ranged between 73 and 88% for patients with cancer pain.[15,16] Of the chronic non-cancer pain patients, 24.8 to 43% report not receiving treatment (*tables 4 and 5*).

What treatment do they receive?

A substantial proportion of the patients receive drug treatment for their pain. Rates vary between 21.6% for any chronic low back pain[14] up to 58% for any chronic neck pain[17] and 61% among nursing home residents with any pain,[18] the majority of patients receiving NSAIDS.

A significant number of patients reported the use of a range of different non-pharmacological interventions such as physiotherapy, acupuncture and postural advice (*table 4*).

Table 3. *Quality of studies included in this review*

Name of first author, publication date	Adequate description of study design and setting	Adequate description of eligibility criteria	Study population is representative of target population	Adequate description of outcomes, exposures, predictors	Adequate description of statistical methods	Adequate description of study participants	Adequate description of losses to follow-up	Results reported as unadjusted and confounder-adjusted including precision	Overall quality
Alonso 2004[30]	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	High
Boonen 2005[23]	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Medium
Borghouts 1999[17]	Unclear	Yes	Unclear	Yes	Yes	Yes	NA	No	Medium
Borghouts 1999[24]	Yes	Unclear	Yes	Yes	Yes	No	NA	Unclear	Medium
Borgsteede 2007[9]	No	No	Unclear	Yes	No	No	NA	No	Low
Breivik 2006[3] / Pain in Europe 2003[31]	Yes	No	Unclear	Yes	No	Yes	NA	No	Low
De Mos 2007[11]	Yes	Yes	Yes	Yes	No	Yes	NA	No	Medium
Demyttenaere 2007[21]	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Medium
De Wit 1999[15]	Unclear	Unclear	No	Yes	No	Yes	NA	No	Low
Dieleman 2008[10]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Medium
Enting 2007[16]	Yes	Unclear	No	Unclear	No	No	NA	No	Low
Huisstede 2008[22]	Yes	No	Yes	Yes	Yes	Yes	NA	No	Medium
Kemler and Furnée 2002[25]	Unclear	Yes	Unclear	Yes	Unclear	Yes	NA	No	Low
Kerssens 2002[6]	Yes	Unclear	Yes	Yes	Yes	Unclear	NA	No	Medium
Lame 2005[19]	Yes	No	Unclear	Yes	Unclear	Yes	NA	Unclear	Low
Opstelten 2002[13]	Yes	Yes	Unclear	Yes	Yes	No	NA	Yes	Medium
Picavet & Hoeymans 2004[20]	Yes	No	Yes	Yes	Yes	No	NA	Yes	Medium
Picavet & Schouten, 2003[7]	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	High
Rupp 2006[32]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Medium
Smalbrugge 2007[33]	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Medium
Steenstra 2006[12]	Yes	Unclear	Yes	Yes	Yes	No	NA	No	Medium
Van den Beuken-Van Everdingen 2007[8]	Yes	Yes	Unclear	Yes	Yes	Yes	NA	Yes	High
Van Herk 2009[18]	Yes	Unclear	Unclear	Yes	No	Yes	NA	Unclear	Low
Van Tulder 1998[14]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium

NA = not applicable.
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Is treatment adequate?

Overall, 34 to 79% of the patients believe their pain is inadequately treated (*tabel 5*). In contrast, another study examined satisfaction for pain treatment among a group of nursing home residents with pain and found 60.3% to be satisfied while 21.2% were not.[18]

IMPACT OF CHRONIC PAIN

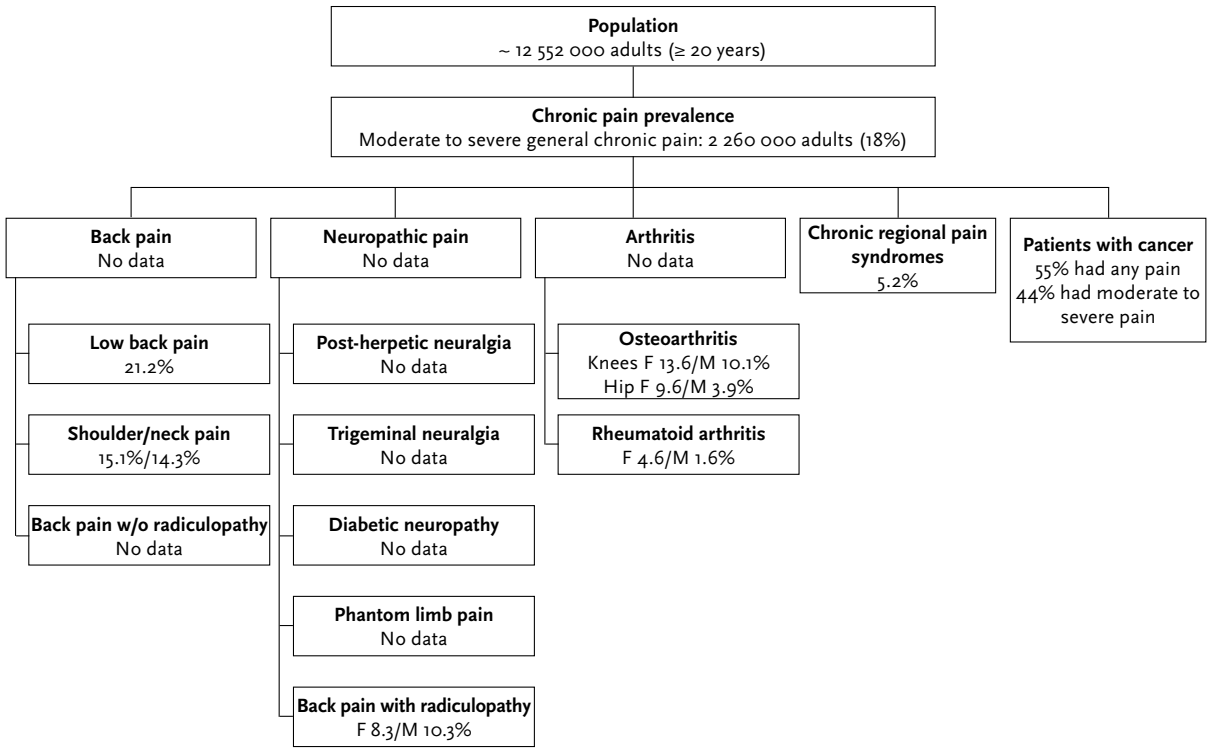
Tables 6 and 7 present the results of impact of pain on quality of life, activities of daily living (ADL), occurrence of mental diseases and days off work in Dutch chronic pain patients.

The impact of chronic pain on quality of life differs in the two studies using the Rand-36 (or SF-36) questionnaire. Patients with any non-cancer chronic pain, referred to a multidisciplinary university pain management clinic, reported a profound impact on quality of life with lowest quality on the 'role limitations physical' dimension.[19] Impact on quality of life among participants with chronic musculoskeletal pain was less, with the highest impact on the vitality dimension.[20]

Chronic pain also affects ADL and mental health. A study examining persons with moderate to severe chronic pain showed that 54% cannot function normally, that 46% cannot take care of themselves and other people and 19% report being diagnosed with depression.[3] Demyttenaere *et al.*[21] showed that some mental disorders (major depressive episode, dysthymia, generalised anxiety disorder and posttraumatic stress disorders) are significantly more prevalent in a group of persons with chronic neck or back pain compared with persons without such pain.

Chronic pain results in workdays lost. Breivik *et al.*[3] reported that on average 8.6 days were lost from work in the past six months in a group of persons with moderate to severe chronic pain. Two other studies reported on absenteeism due to chronic neck pain and found that about 15% were absent for at least a week due to chronic complaints of neck, shoulder and arm[22] and 20% in a sample with chronic neck pain.[17]

Figure 1. *Prevalence rates of specific pain disorders and cancer pain*[3,7,8]



F = females; M = males

One study reported direct medical and indirect costs due to three chronic disorders.[23] The total annual costs per patient were €7814 for fibromyalgia (17% direct medical costs), €8533 for chronic low back pain (13% direct medical costs) and €3205 for ankylosing spondylitis (32% direct medical costs). In 1996 costs due to any neck pain were $686.2 million, of which 77% was used for indirect medical costs.[24] Kemler and Furnee[25] reported that having chronic pain results in a decrease of net yearly income and additional costs. Mean out-of-pocket expenses related to CRPS of €1350 per patient per year were reported.

One study was found that reported on any impact of cancer pain on several aspects of quality of life.[16] Impact of pain was highest for daily activities and work and lowest on relations. No studies were found reporting on impact on ADL, depression, days of work and costs.

DISCUSSION

We performed a best-evidence review using principles of systematic reviewing on epidemiology of chronic pain in the Netherlands, and focused on prevalence/incidence of chronic pain, treatments given and impact of such pain. For each question, we selected the three or four best studies based on criteria of representativeness, size, recency and study quality. This review illustrates that chronic pain is a common problem among adults with a prevalence up to 44% for chronic musculoskeletal pain and 18% for moderate to severe general chronic pain. A substantial proportion of patients with chronic pain reported to receive no treatment (24.8 to 43%). Of those who get treatment, a considerable number feels their pain is not adequately controlled. Chronic pain has a negative impact on quality of life, ADL, mental status, and is associated with sick leave and high direct and indirect medical costs. There is some evidence that the above findings also apply for chronic cancer pain but this topic is poorly researched. Chronic pain deserves to be viewed as an important public health problem which warrants attention from healthcare workers and policy makers.

We identified a fair number of studies. However, in general the quality was poor, mainly because the representativeness of the examined population was unclear, and results were typically presented descriptively without adjustment for confounders. Also, many studies relied on self-reported pain which lacks confirmation of the diagnosis.

An important problem in interpreting the results of this review lies within the patient population of chronic pain. First, chronic pain is not considered to be a disease and therefore it is not registered as a separate entity in GP registries / hospitals. Therefore, hospital or GP practice based studies report on chronic pain in a healthcare-

Table 4. *Treatments received by patients with chronic pain*

Description of chronic pain	% of the patients that get treated	Frequencies of drug treatment (for pain)	Frequencies of non-drug treatment
General / non-cancer pain			
Moderate to severe chronic pain (Breivik et al. 2006; Pain in Europe 2003)[3 31]	57%	• 41% prescription medication • NSAIDs: 36% • COX 2 inhibitor: 16% • Weak opioids: 14% • Paracetamol: 11% • Strong opioids: 5%	Ever physiotherapy: 52% Ever acupuncture: 21% Ever massage: 17% Tried exercise: 14% Tried heat: 8% Tried herbal supplements: 7% Tried relaxation: 6% Tried support groups: 4% Tried nerve stimulation: 4% Tried ointments/creams: 4% Tried diet/special foods: 4%
Any general pain (incl non-chronic) in nursing home residents (Van Herk et al. 2009)[18]	61%	• Non-opioids: 42.5% • weak opioids: 8.5% • strong opioids: 10.5%	Not reported
Any chronic low back pain patients visiting their GP (Van Tulder et al. 1998)[14]	74%	Pain medication (any): 21.6% (95% CI 17.9, 25.3) • Paracetamol/aspirin: 3.9% (95% CI 2.3, 6.2) • NSAID: 16% (95% CI 12.8, 19.8) • Benzodiazepine: 3.3% (95% CI 1.8, 5.5) • Other medication: 0.7% (95% CI 0.1, 2.0)	Heat application: 4% (95% CI 2.4,6.2) (Bed)rest: 5.7% (95% CI 3.8, 8.2) Injection: 0.4% (95% CI 0.05,1.5) Postural advice: 6.1% (95% CI 4.1, 8.7) Work advice: 1.3% (95% CI 0.5, 2.7) Other treatment: 3% (95% CI 1.6, 4.9)
Any chronic neck pain patients visiting their GP (Borghouts et al. 1999)[17]	69%	Pain medication: • Paracetamol/aspirin/NSAID: 58% • Benzodiazepine: 10% • Antidepressants: 3% • Other medication: 8%	Heat application: 20% (Bed)rest: 11% Postural advice: 18% Collar: 3% Other treatment: 3%
Any general neuropathic pain (incl non-chronic pain) (Dieleman et al. 2008)[10]	53%	NSAIDs: 34.7% Benzodiazepines: 11.9% Sedative/hypnotics 9.1% Opioids: 6.6%. Anticonvulsants: 4.8% Tricyclic antidepressants : 4.7%	Not reported
Cancer pain			
Any chronic cancer pain (De Wit et al. 1999)[15]	88.2%	Non-opioids: 71.6% • Alone (WHO step I): 27.2% • in combination with WHO II/III/IV: 72.8% Weak or strong opioids: 69% • Alone : 24.5% • In combination with non-opioids: 75.5% • Weak opioids in combination with non-opioids: 94.1% • Strong opioids in combination with non-opioids: 57.9% Strong opioids (WHO step III/IV): 36.4% Parental medication (WHO step IV): 10.9%	Radiation therapy: 15.0% Chemotherapy: 12.1% Surgery: 2.6% Hormonal therapy: 1.6% Treatments such as nerve blocks or TENS: 3.6% Non-drug treatments: 89.9% • Positions/movements: 81% • Distraction: 45.7% • Use of heat or cold: 34.6% • Relaxation: 22.8% • Massage: 15.8% • Other: 11.9%
Any cancer pain (Van den Beuken-van Everdingen et al. 2007)[8]	Not reported	WHO step I: 15% WHO step II: 6% WHO step III: 7% Co-analgesics: 7%	Not reported
Any cancer pain (Enting et al. 2007)[16]	73%	73% (95% CI 68, 79%)	Not reported

GP = general practitioner; NSAIDs = non-steroid anti-inflammatory drug; CI = confidence interval; WHO = World Health Organization.

seeking population and hence a cause for the pain is searched for. In population-based studies, the prevalence of pain is influenced by a lack of gold standard for the diagnosis. Second, most studies focused on certain subpopulations, i.e. chronic low back pain, fibromyalgia, chronic repetitive strain injury (RSI). This results in a heterogeneous population in our review leading to dispersed results on prevalence/incidence, care seeking and impact of pain.

We found variation in the prevalence of chronic pain. This is a known problem in this field and may partly be explained by differences in the definition and classification

Table 5. *Patients with chronic pain that are untreated, inadequately treated and satisfaction of treatment*

Description of chronic pain	Untreated (%)	Inadequately treated	Satisfied (self-report)
General / non-cancer pain			
Moderate to severe general chronic pain (Breivik et al. 2006; Pain in Europe 2003)[3,31]	43%[1]	79%[3]	*Not selected for this research question*
Any general pain in nursing home residents (including non-chronic pain)(Van Herk et al. 2009)[18]	36%[2]	Opioids: 69.2%[4] Paracetamol : 30.8%[4]	*Not selected for this research question*
Any general pain in nursing home residents (including non-chronic pain) Subgroups: - those with moderate pain - those with severe pain	24.8%[2] 22% 29%	34%[5]	60.3%
Any chronic neck pain patients visiting their GP (Borghouts et al. 1999)[17]	31%[1]	*Not selected for this research question*	*Not selected for this research question*
Any chronic low back pain patients visiting their GP (Van Tulder et al. 1998)[14]	36%[1]	*Not selected for this research question*	*Not selected for this research question*
Cancer pain			
Any cancer pain (Enting et al. 2007)[16] For around the clock medication	*Not selected for this research question*	65% (95% CI 59, 71%)[5]	*Not selected for this research question*
Any cancer pain (Van den Beuken-van Everdingen et al. 2007[8] Subgroups: - patients who received anti-cancer treatment with curative intent ≥6 m ago - patients receiving anti-cancer treatment with curative intent or last treatment < 6 m ago - patients receiving palliative anti-cancer treatment - treatment not or no longer feasible	*Not selected for this research question*	45% (95% CI 36, 54%)[5] 73.6%[4] 81% 83.9% 70.6% 29.5%	*Not selected for this research question*
Cancer patients with chronic pain (De Wit *et al.* 1999)[15]	*Not selected for this research question*	*Not selected for this research question*	65.7% (11.3% were neither satisfied or dissatisfied and 12.3% were dissatisfied)
Subgroup of patients with moderate to severe pain			67.9%

1 Not receiving treatment for their pain in any way; 2 Not receiving analgesics; 3 Positive response to the question ''Are there ever times when your pain medicine is not adequate to control your pain?'; 4 Prescribed Daily Dose/Defined Daily Dose ratio (PDD/DDD-ratio) below 2/3; 5 Indicated by negatives scores on the Pain Management Index.

of pain and study methods.[1,2,6] Studies on incidence of chronic pain were very sparse and were limited to the incidence of specific chronic conditions such as neuropathic pain and complex regional pain syndrome. Estimates of prevalence or incidence of any chronic pain in the Dutch population are hampered by the fact that pain is not considered to be a separate entity and therefore not registered as such in registries.

Although the prevalence varied, it is clear that the prevalence of chronic pain is much higher than the prevalence of any other chronic disease in the Netherlands, such as diabetes (in 2003, about 600,000 persons were diagnosed with diabetes in the general practice),[26] and coronary heart disorders (estimated prevalence in 2007 was between 300,000 and 1,000,000).[27] The prevalence of cancer is estimated at 400,000 persons in the Netherlands, which is about 2.5% of the population.[28]

Chronic pain has a negative impact on quality of life. In addition, chronic pain is associated with problems such as difficulties with ADL, depression and other mental health disorders which may further decrease quality of life. An effective treatment may help break through such a vicious circle and affect the life of persons with chronic pain in several ways. Chronic pain was also shown to influence the income of persons and their spouses in a negative way.[25]

Costs of chronic pain are not well researched. The most recent study used data from 2002 and showed substantial direct and indirect medical costs for three chronic diseases: fibromyalgia, chronic low back pain and ankylosing spondylitis.[23] The study on neck pain, although representative for the whole Dutch population, includes both acute and chronic neck pain and was based on data of at least ten years ago.[24] Therefore the complete burden of chronic pain is unclear from these studies.

In summary, chronic pain occurs frequently, has a negative impact for the patient and society and treatment may not always be adequate. Increasing the accessibility to adequate treatment for all chronic pain sufferers will reduce the negative consequences of it on individual and public health level. Therefore, chronic pain deserves to get more attention from all the stakeholders who are involved in chronic and oncological pain, such as Dutch healthcare workers and policy makers. Defining chronic pain in the Netherlands as a separate and important public health problem may make Dutch healthcare workers and policy makers more vigilant to this health problem.

Table 6. *Impact of chronic pain on quality of life*

Description of chronic pain	Impact on quality of life
Any non-cancer chronic pain (Lame et al. 2005)[19]	Dimensions of Rand-36* questionnaire, mean (SD): Physical Functioning: 41.3 (26.3) Social Functioning: 39.9 (27.0) Role Limitations Physical: 9.7 (24.3) Role Limitations Emotional: 46.6 (46.1) Mental Health: 56.7 (22.6) Vitality: 39.8 (20.4) Bodily Pain: 24.6 (17.9) General Health Perception: 44.7 (21.4)
Any chronic arthritis (Alonso et al. 2004)[30]	Persons with any chronic arthritis scored: 4.1 points lower than respondents without chronic conditions (who scored 53.4) on the Physical Summary Component of the Rand-36 1.0 point higher than respondents without chronic conditions (who scored 55.2) on the Mental Summary Component of the Rand-36
Any chronic musculoskeletal pain (Picavet and Hoeymans 2004)[20]	Dimensions of Rand-36 questionnaire, scores (SD): Physical Functioning: 82.5 (24.8) Social Functioning: 84.2 (23.1) Role Limitations Physical: 77.7 (37.8) Role Limitations Emotional: 87.2 (30.6) Mental Health: 77.3 (17.1) Vitality: 65.9 (20.0) Bodily Pain: 80.2 (23.6) General Health Perception: 69.4 (19.6) EQ-5D: % with any problem (SD) Mobility: 19 (43) Self care: 4.2 (22.7) Usual activities: 22.2 (43.1) Pain/discomfort: 45.2 (50) Anxiety/ depression: 18.6 (39.3)
Any cancer pain (Enting et al. 2007)[16]	Impact of pain on (percentage of patients reporting very much or quite a bit of interference): Daily activities: 51% Work: 47% Sleep: 41% Mood: 35% Enjoyment: 35% Walking: 34% Relations: 17%

*** score from 0-100, a higher score representing better quality of life.**

CONFLICTS OF INTEREST

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Table 7. *Impact on ADL, depression, days off work and costs*

Population	Impact on ADL	Impact on depression	Impact on days off work	Cost
Moderate to severe general chronic pain (Breivik et al. 2006[3]/ Pain in Europe 2003) [31]	54% cannot function normally 46% cannot take care of themselves and other people	19% reported being diagnosed with depression	Mean time lost from work in the past 6 months: 6.8 days	*Not selected for this research question*
Any chronic pain in neck, shoulder and arms (Huisstede et al. 2008) [22]	38.3% limitation in daily life	*Not selected for this research question*	Absenteeism among those employed: < 1 week: 7.8% 1-4 weeks: 7.5% >4 weeks: 7.8%	*Not selected for this research question*
Any chronic neck pain patients visiting their GP (Borghouts et al. 1999) [17]	*Not selected for this research question*	*Not selected for this research question*	Absenteeism among those employed: <1 week: 13% >1 week: 20%	*Not selected for this research question*
Any neck pain (Borghouts et al. 1999) [24]	*Not selected for this research question*	*Not selected for this research question*	*Not selected for this research question*	Society cost (1996): $686.2 million Direct medical costs: 23% Indirect medical costs: 77%
Any chronic neck and back pain (Demyttenaere et al. 2007)[21]	*Not selected for this research question*	Prevalence of mood disorders: persons without versus with chronic back/neck pain: Major depressive episode: 4.4 vs 9.4% Dysthymia: 1.2 vs 4.5% Generalised anxiety disorder: 0.8 vs 2.1% Agoraphobia or panic disorder: 1.7 vs 1.7% Social phobia: 1.0 vs 2.4% Posttraumatic stress disorder: 1.4 vs 7.4% Alcohol abuse/ dependence disorders: 1.7 vs 1.7%	*Not selected for this research question*	*Not selected for this research question*
Any rheumatoid arthritis (Rupp et al. 2006)[32]	Disability measured with the validated Dutch questionnaire capacities of daily life*: mean score (SD): 0.66 (0.62)	Dimensions of Rand-36 questionnaire, scores (SD): Mental summary component scale: 49.2 (11.4)	*Not selected for this research question*	*Not selected for this research question*
Any fibromyalgia pain, any chronic low back pain and any ankylosing spondylitis pain (Boonen et al. 2005)[23]	*Not selected for this research question*	*Not selected for this research question*	*Not selected for this research question*	Total annual costs per patient: fibromyalgia: €7814 (17% direct medical cost) chronic low back pain: €8533 (13% direct medical costs) ankylosing spondylitis: €3205 (32% direct medical costs)
Any chronic regional pain syndrome (Kemler and Furnée (2002)[25]	*Not selected for this research question*	*Not selected for this research question*	*Not selected for this research question*	Mean net yearly income decreased for : single: $8500 to $5500 male patients: $26,000 to $22,000 female patients: $24,500 to $22,500 Mean out-of-pocket expenses related to chronic regional pain syndrome: $ 1350 /patient / year.

***This questionnaire consists of 20 items measuring the degree of difficulty a patient has in performing activities of daily living (ADL) in 8 areas (dressing and grooming, arising, eating, walking, hygiene, gripping, reaching, and other activities). Responses to each item can range from 0 (no difficulty) to 3 (unable to do). The score is not influenced by the use of aids needed for certain ADL. The scores of each item were averaged to create an overall mean score (range 0–3, higher scores indicating more disability).**
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ERRATUM

Unfortunately in the article 'Longterm follow-up of organ-specific antibodies and related organ dysfunction in type 1 diabetes mellitus' by L.C.G. de Graaff et al., which was published in Neth J Med. 2011;69(2):66-71, an error was made in printing table 1. The correct table is printed here.

We apologise for any inconvenience.

Table 1. *Prevalence of organ-specific antibodies and corresponding organ dysfunction in 396 DM1 patients*

Antibodies	**Tg-Ab**		**TPO-Ab**		**Tg- and/or TPO-Ab**			**PCA**			**ACA**	
	-	+	-	+	-	+		-	+		-	+
N (total)	333 (84.1%)#	17 (4.3%)	308 (77.7)#	32 (8.1%)	295 (74.5)#	41 (10.4%)		362 (91.4)#	23 (5.8%)		392 (98.9)#	2 (0.5%)
% F	42%	71%**	42%	78%**	41%	76%**		45%	70%*		46%	100%
Age (baseline)	43.4 ±12.9	45.8 ±10.7	43.2 ±12.9	45.3 ±10.5	43.1 ±13.0	45.4 ±11.1		43.6 ±12.5	43.4 ±17.7		43.6 ±12.8	59.0 ±17.0
DM duration (baseline)	22.4 ±10.0	22.6 ±10.0	22.5 ±10.0	21.7 ±11.1	22.4 ±10.1	22.5 ±11.2		22.7 ±10.2	21.9 ±12.2		22.7 ±10.4	27.5 ±26.2
Organ dysfunction (total)	11.7%	60.0%	9.4%	53.4%	9.1%	52.9%		9.7%	60.9%			
Subclinical hypothyroidism	0.8%	13.3%	0.9%	11.5%	0.9%	14.7%	Macrocytosis	1.4%	4.3%	Hypocortisolism	2.4%	0
Clinical hypothyroidism	5.5%	33.3%	4.3%	30.8%	3.6%	29.4%	Macrocytic anaemia	0.3%	4.3%	Hypercortisolism	4.9%	0
Hyperthyroidism	3.1%	0	1.7%	3.8%	1.8%	2.9%	Pernicious anaemia	0.3%	8.7%			
Graves	2.3%	13.3%	2.6%	7.7%	2.7%	5.8%	Normocytic anaemia	5.1%	26%			
							Microcytic anaemia	2.6%	17.4%			
Diagnostic accuracy	NPV 0.88	PPV 0.60	NPV 0.91	PPV 0.53	NPV 0.91	PPV 0.53		NPV 0.90	PPV 0.61			
AB+ vs AB -	p<0.001		p<0.001		p<0.001			p<0.001			NS	

Data are presented as mean ± SD unless stated otherwise * p<0.05 ** p<0.01, # total patient numbers do not add up to 396 since weakly positive patients were left out of the analysis; Tg-Ab = antibodies against thyroglobulin; TPO-Ab = antibodies against thyroid peroxidise; PCA = antibodies against parietal cells; ACA = antibodies against adrenal cortex; F = female; DM = diabetes mellitus; hyperthyroidism = hyperthyroidism without thyroid stimulating antibodies; Graves = Graves' disease; PA = pernicious anaemia; Addison = Addison's disease; PPV = positive predictive value; NPV = negative predictive value; AB^+ vs AB^- = level of significance for the difference in organ dysfunction frequency between AB-positive and AB-negative patients.

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LETTER TO THE EDITOR

Surviving a life-threatening 2,4-DNP intoxication: '*Almost dying to be thin*'

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Dear Editor,

To our knowledge, all case reports including the most recent ones describe patients who die following a 2,4-dinitrophenol (DNP) intoxication.[1,2] DNP was used extensively as a diet aid, but was taken of the market because of serious adverse effects. Nevertheless, it's readily available over the internet. We present a case in which immediate and aggressive treatment led to complete recovery.

We describe an alert, excessively sweating, tachypnoeic and tachycardic woman who readily admitted ingestion of DNP in excess of 600 mg. Toxicology screening was positive for diazepam, fluoxetine and cannabinoids. She developed a progressive hyper-metabolic state. Temperature at admission was 37.5 °C and quickly rose to 39.1 °C. Mild rigidity developed. Mildly elevated liver enzymes and rhabdomyolysis were present (creatine kinase (CK) 18,170 U/l). The fatal outcome in serial case reports convinced us to employ an aggressive strategy. Active cooling (hypothermia blanket, target temperature 37 °C) and fluid resuscitation was initiated immediately, followed by sedation and intubation because of progressive respiratory failure. Dantrolene (1 mg/kg) was given intravenously and repeated several times in the first 24 hours. No side effects occurred. Active cooling was terminated after four days when the CK levels decreased. Following transient renal failure, the patient ultimately made a full recovery.

DNP uncouples oxidative phosphorylation in the mitochondria resulting in rapid energy consumption without generation of ATP. Hyperthermia and many other (fatal) sequelae can ensue.[3] Denial by the patient and unawareness of the popularity of DNP as a diet aid and the clinical manifestations of a potential lethal intoxication may hamper the diagnosis of DNP intoxication. Acute ingestion of 10 to 20 mg/kg can be fatal.[3] Any measure to minimise peak absorption fails unless it takes place immediately following ingestion. DNP is also not amenable to dialysis. Early recognition of a severe intoxication is essential. Acute supportive management, most importantly rapid cooling (with intravenous sedation and intubation if necessary), is vital. Dantrolene is an important therapeutic adjunct.

DNP is a relatively unknown toxic compound. It's lethal potential warrants vigilance and aggressive therapy in recognized and suspected cases.

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INFORMATION FOR AUTHORS

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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