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EDITORIAL

Hepatitis C: many small steps

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Surprisingly few researchers have managed to produce an electron micrograph of hepatitis C virus (HCV).[1,2] Of course, we do not doubt the existence of HCV. The discovery of HCV was a milestone for molecular biology and virology. For the first time, the application of molecular genetic techniques led to the discovery and description of a human pathogen. In the late 1980s Houghton and colleagues studied plasma of a chimpanzee, highly infectious for 'non-A, non-B hepatitis'. Applying blind expression cloning of a cDNA library, obtained from the chimpanzee plasma, the '5-1-1' protein was obtained, which was recognised by antibodies of a well-characterised chronic non-A, non-B hepatitis patient.[3,4] The recognition of non-A, non-B hepatitis in clinical practice predates the discovery of its cause by many years.[5] It has been estimated that in the 1960s, one in five patients receiving blood transfusions in the USA acquired non-A, non-B hepatitis.[6] The Nixon administration improved this situation markedly by promoting the collection of blood among unpaid volunteers, instead of using prisoners and paid donors as the source of blood. Following the identification of HCV, assays were developed for the detection of HCV antibodies and HCV RNA, enabling the diagnosis of hepatitis C in patients and the screening of blood donors. Nevertheless, the diagnosis of acute hepatitis C remains tricky because specific antibodies may still be absent in a recently infected patient. The diagnosis of acute recent hepatitis C must be based on detection of HCV RNA. Regarding the safety of blood transfusion in the Netherlands, the screening of each blood donation for both HCV antibodies and HCV RNA has decreased the risk of transmission of HCV to less than 1 per 10 million donations.[7]

What is the global burden of HCV? The World Health Organisation estimates 170 million persons to be chronically infected with HCV. For comparison: 450 million persons are thought to carry hepatitis B virus. Locally the HCV/HBV ratio may be different. In Amsterdam, random sampling of the population enabled Baaten and colleagues to calculate the number of Amsterdam citizens chronically infected with HCV or HBV to be 3709 and 2453 respectively.[8] You may grow old without knowing you are infected with HCV, but guidelines agree that treatment of HCV infection must be considered for each HCV-infected person.[9,10] In the long run a significant but poorly defined number of patients will develop significant liver disease: intermittent or chronic hepatitis; and cirrhosis in 5 to 25% of patients over a period of 25 to 30 years. Subsequently, HCV-induced cirrhosis introduces the risk for hepatic decompensation (in 30% over 10 years) and hepatocellular carcinoma (in 1 to 3% per year).[10] In this issue of *The Netherlands Journal of Medicine,* Vlaar and colleagues describe that HCV-associated malignancy is not limited to hepatocellular carcinoma: HCV may induce cholangiocellular carcinoma or B-cell lymphoma.[11] They warn to be aware of HCV-associated B-cell lymphoma, especially when patients have HCV-associated mixed cryoglobulinaemia and incomprehensibly high serum levels of lactate dehydrogenase.

Several studies demonstrate that hepatitis C is not a sexually transmitted disease (STD).[12,13] As an exception to this rule, HCV has recently become an STD among HIV-infected men having sex with other HIV-infected men. Transmission of HCV during birth or via breast feeding is rare. Arthropod-borne transmission of HCV and an animal reservoir have not been found. How then is it possible that HCV maintains its existence as a human pathogen? We must conclude that HCV solely depends on parenteral blood-borne transmission between humans. This is less odd than it seems. World-wide, native tribes perform body piercing and ritual or beautifying tattooing and scarification. This practice is old: over 50 tattoos were observed on Ötzi the iceman, whose mummified body was found 5300 years after his death, in a glacier on the border between Austria and Italy. In the 20th century the popularity of tattooing probably waned. Luckily for HCV, three very efficient parenteral ways of transmission took over: the wide spread use of blood transfusion and

blood products; intravenous drug abuse; and insufficient sterilisation of medical equipment. When donor screening for HCV was introduced in the Netherlands in 1991, over 200 regular donors were found to carry HCV. During many decades this cohort of donors must have infected thousands of patients, especially via pooled blood products such as clotting factor. It appeared that in 1991 all haemophilia patients had already been infected with HCV. The consequences of the historical and ongoing use of unsterile medical equipment cannot be underestimated. Attributed to this cause, currently 9.8% of Egyptians are chronically infected with HCV.[14]

Hepatitis C is not only an outlier regarding its discovery and transmission, it is the only major chronic virus infection that can be cured. Modern antiviral treatment, based on the daily oral administration of ribavirin and weekly subcutaneous injection of pegylated interferon, results in a cure rate of 50% in patients infected with HCV genotype 1 or 4, and 80% in patients infected with HCV genotype 2 or 3.[9] This success was obtained via small, incremental improvements in the antiviral regimen for HCV. In the early 1990s, HCV therapy consisted of the injection of interferon 3 MU, three times a week, for 48 weeks. This regimen caused sustained response in only 9% of genotype 1 infections and in 30% of genotype 2 or 3 infection. Ribavirin as monotherapy for HCV has no effect on HCV replication, but added to interferon (since 1998) it is synergistic, with clearance of HCV in 30 and 60% of cases, respectively. Since 2002 interferon has been replaced by a pegylated form of interferon which shows increased blood levels over a longer period of time, and thus can be injected once per week. Notwithstanding this success, we still do not know what we are doing: the mechanism of action of interferon and ribavirin in curing HCV remains unknown.[15] Interferon obviously 'modulates the immune response' while ribavirin may 'push HCV over the mutation threshold'.

In this issue of *The Netherlands Journal of Medicine*, Gevers and colleagues introduce an additional step in the gradual improvement of HCV therapy.[16] They report that HCV genotype 1 infected patients, with a slow response to peginterferon plus ribavirin treatment, benefit from a prolonged treatment of 72 instead of 48 weeks. This improved regimen may be short-lived. In the course of 2011 the registration of two HCV protease inhibitors (telaprevir and boceprevir) is foreseen. For HCV genotype 1 infection, triple therapy consisting of peginterferon plus ribavirin plus telaprevir or boceprevir is expected to boost the cure rate, while at the same time the duration of treatment may be decreased.

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REVIEW

Malignancies associated with chronic hepatitis C: case report and review of the literature

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ABSTRACT

Hepatocellular carcinoma (HCC) is a well-known consequence of hepatitis C virus (HCV) infection mainly in cirrhotic patients. Associations of other malignancies such as cholangiocellular carcinoma and B-cell malignancies with HCV are less well known. Here we review pathophysiological aspects of malignancies associated with HCV infection. A case report of HCV-related HCC and B-cell lymphoma illustrates the increased risk for HCV-infected patients to develop other malignancies besides HCC.

KEYWORDS

Hepatitis C, lymphoma, cryoglobulinemia, hepatocellular carcinoma, cholangiocellular carcinoma

INTRODUCTION

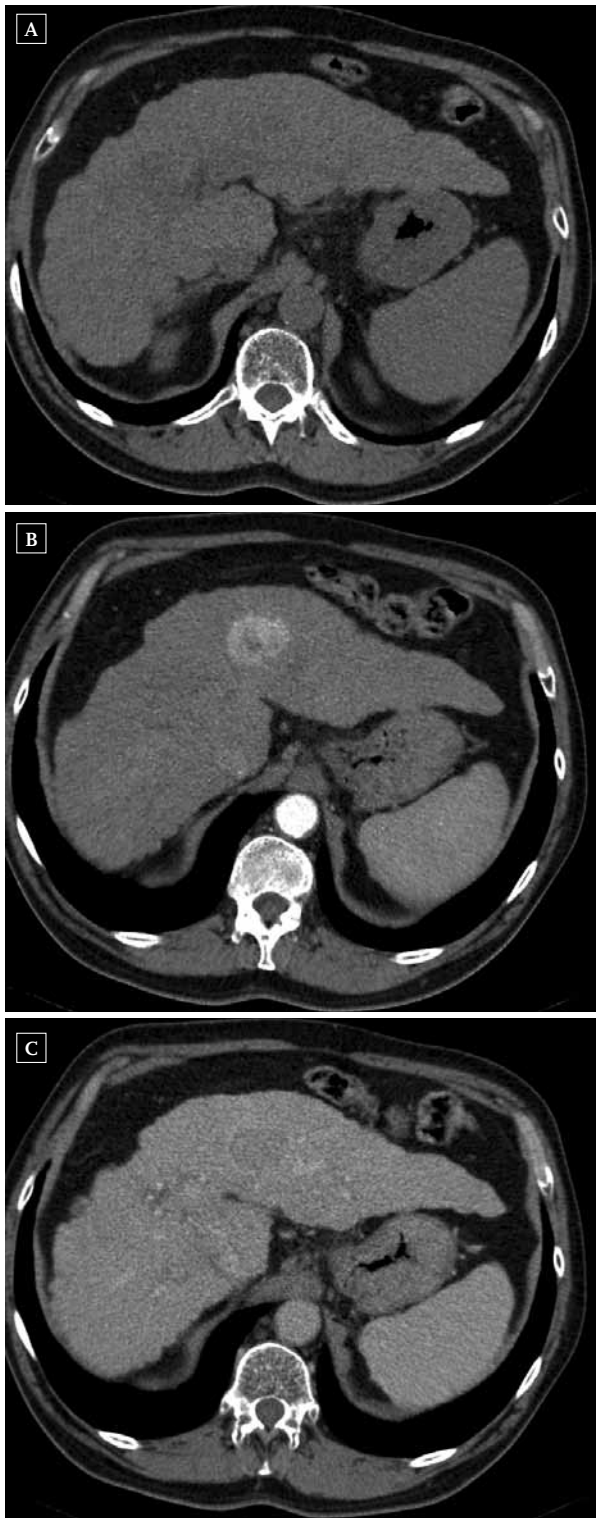
Up to 25% of patients with chronic hepatitis C virus (HCV) infection are known to develop cirrhosis after 25 to 30 years, with a 1 to 4% annual risk to develop hepatocellular carcinoma (HCC).[1] Thus, treatment strategies are directed towards hindering disease progression, hepatic decompensation and development of HCC. There is less awareness of other malignancies associated with HCV infection such as cholangiocellular carcinoma and mixed cryoglobulinaemia (MC) with subsequent progression to B-cell non-Hodgkin's lymphoma (NHL), which may be under-reported and possibly underdiagnosed in HCV-infected patients.[2-4]

HCV infection has been implicated as the major aetiological factor sustaining B-cell clonal expansion in type II MC.[5] Furthermore, it has been speculated that HCV has a pathogenetic role in the development of MC-associated B-cell malignancies.[6] We report on a patient who developed HCC and B-cell lymphoma after successful eradication of HCV. We review the literature on pathophysiological aspects of malignancies associated with HCV infection.

CASE REPORT

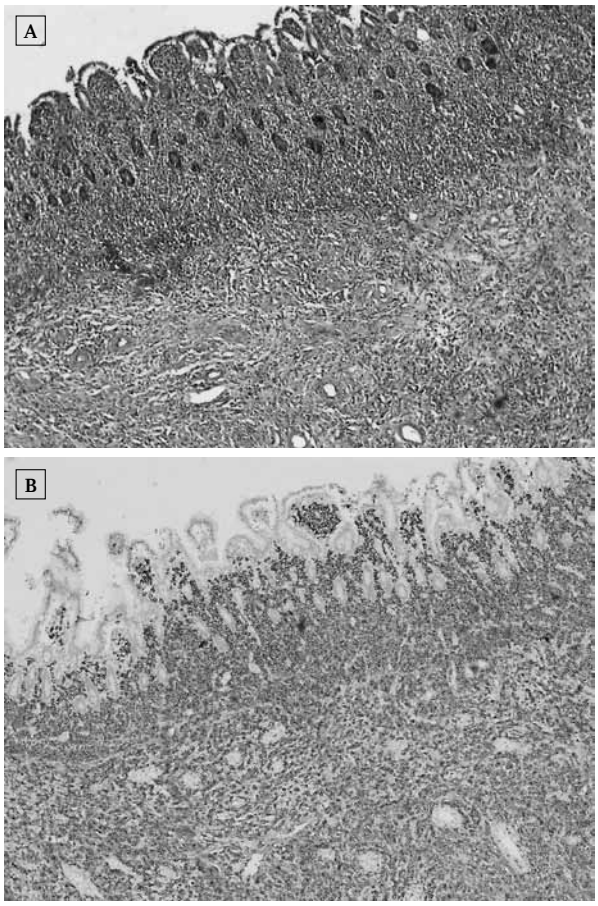
A 73-year-old man presented at our emergency department with severe abdominal pain and shock. The patient was known with Child-Pugh A cirrhosis associated with HCV infection, genotype 2, which was successfully eradicated two years before with peginterferon and ribavirin. Further history of this patient revealed diabetes mellitus type 2, cholelithiasis and prepyloric ulcers. During routine screening of the cirrhotic liver two lesions had been identified in liver segment IV which fulfilled the criteria for hepatocellular carcinoma (HCC) when dynamic imaging techniques were applied *(figure 1)*. The serum alpha-fetoprotein was not elevated. The patient had undergone transarterial chemoembolisation (TACE) of the tumours with doxorubicin and microbeads three months before admission. Additional radio frequency ablation (RFA) was planned because of residual tumour tissue after TACE treatment. However, due to myocardial ischaemia during the last admission, the patient had been discharged to a nursing home to fully recover before performing RFA. Laboratory investigation showed a haemoglobin level of 6.0 mmol/l, mean corpuscular volume of 82.7 fl, platelet count of 246 x 10^9/l, leukocyte count of 10.4 x 10^9/l, a monoclonal paraprotein (positive M-protein with IgA 4.81 g/l, IgG 16.0 g/l and IgM 0.8 g/l), and an elevated lactic dehydrogenase (>1000 U/l) in the last three months. No signs of vasculitis were described by the treating physician. On presentation at our emergency department, ascites analysis disclosed a high leukocyte count and infection

Figure 1. *Hepatocellular carcinoma as indicated by dynamic CT scan in a 73-year-old man with chronic HCV infection two years after effective treatment with peginterferon and ribavirin*



The protocol for investigating the presence of hepatocellular carcinoma includes infusion of an intravenous contrast agent and subsequent three-phase scanning: (a) before contrast administration, (b) immediately after contrast administration, and (c) after a delay of four minutes. The three images show the typical pattern of a hepatocellular carcinoma with (b) arterial hypervascularisation immediately after contrast administration, and (c) washout of contrast in one of the delayed phase studies.

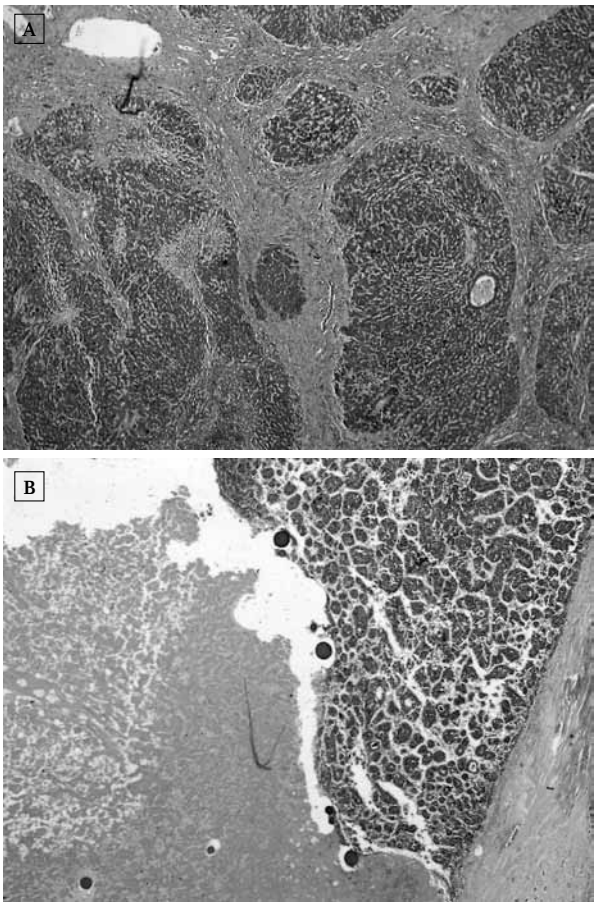
Figure 2. *Large B-cell lymphoma in a 73-year-old man with chronic HCV infection two years after effective treatment with peginterferon and ribavirin*



(a) The small bowel wall after resection shows a diffuse infiltrate of large atypical lymphoid cells: haematoxylin and eosin staining (40x). (b) CD20 immunohistochemical staining (40x) demonstrates the B-cell origin of these cells consistent with a large B-cell lymphoma, best classifiable as diffuse large B-cell lymphoma (WHO 4th edition, 2008).

with Gram negative and positive bacteria. CT abdomen was suggestive for intestinal perforation, and lesions suggestive of malignancy were seen in the intestinal wall. Emergency laparotomy confirmed perforation of the small intestine. Resection of the affected intestine and a temporary ileostomy were performed. Pathological examination revealed intestinal large B-cell lymphoma, best classifiable as diffuse large B-cell lymphoma or short diffuse large B-cell lymphoma *(figures 2a* and *b)*. Additional analysis revealed a BCL-6 translocation in the lymphoma but no BCL-2 or c-myc translocation. The patient did not recover and died 15 days after surgery due to multiorgan failure. Autopsy revealed that the B-cell lymphoma was located in the stomach, small intestine, and in the soft tissue around the adrenal gland, but not in the bone marrow or the lymph nodes. HCC was confirmed in the cirrhotic liver *(figures 3a* and *b)*.

Figure 3. *Residual hepatocellular carcinoma after transarterial chemoembolisation in a 73-year-old man with chronic HCV infection two years after effective treatment with peginterferon and ribavirin*



(a) Liver tissue after autopsy (20x) shows severe cirrhosis. (b) Largely necrotic tumour tissue after transarterial chemoembolisation with a small rim of vital hepatocellular carcinoma (40 x, haematoxylin and eosin staining).

REVIEW

Hepatocellular carcinoma and hepatitis C

The risk of developing HCC is 1 to 4% per year for a patient with HCV-related cirrhosis.[7,8] Prevalence of HCV in the general population in the Netherlands is estimated at 0.2 to 0.4%.[9,10] Intravenous drug use, tattooing, and medical procedures such as dialysis and blood transfusion before the era of HCV screening have all contributed to the wide spread of HCV. The delay between HCV infection and HCC development between 10 and 30 years raises the expectation that the number of cases with HCV-related HCC will further rise remarkably during the next decade in Europe,[11] as can be seen in the United States of America.[12] The molecular biological pathways leading to HCC development need to be further unravelled in order to intervene early to prevent HCC development and to treat patients more effectively. The contribution to HCC development of HCV-specific viral characteristics and an individual's specific immune response against HCV infection are interesting lines of investigation.

The current understanding of the pathogenesis of HCC in HCV-infected patients is that continuous hepatic inflammation due to a poor clearance of the virus is a major culprit. The poor clearance is due to an error-prone viral polymerase causing high rates of mutants. At present, a shortage of effective and well-tolerable treatment options still leads to treatment failure in a high number of patients. In addition, difficult-to-treat genotypes represent evolution of interferon resilient viruses.[13] Continuous inflammation results in oxidative cell damage and increased cell turnover, which will induce DNA damage, stimulating carcinogenesis and increasing the risk for development of HCC.[14] In line with this, continuously enhanced hepatocyte turnover due to alcohol exposure, steatohepatitis, autoimmune hepatitis, alpha-1-antitrypsin deficiency, haemochromatosis, or Gaucher's disease, can all result in development of HCC.[15-20] Furthermore, as in various other chronic liver diseases, prevention of cirrhosis in HCV-infected patients, even without viral clearance or normalisation of liver enzymes, lowers the risk of HCC development and improves long-term prognosis.[21,22]

HCC is the most common malignancy associated with HCV infection. However, HCV infection is also associated with two other malignancies which deserve attention.

Cholangiocellular carcinoma and hepatitis C

Cholangiocellular carcinoma is the second most common primary hepatic tumour after HCC.[23] Cholangiocellular carcinomas make up 15% of primary liver cancer worldwide. The incidence is estimated to be 1 to 2 cases per 100,000 population in the US.[24] Primary sclerosing cholangitis is one of the most commonly recognised risk factors for cholangiocellular carcinoma.[25] Cholangiocellular carcinomas are highly fatal tumours, as they are clinically silent until a very late stage in the majority of cases.

Cholangiocellular carcinomas, primarily cancers of the epithelial cells in the bile ducts arising anywhere along the intrahepatic or extrahepatic biliary tree, are relatively rare but high incidence rates have been reported in Eastern Asia, especially in Thailand. An explanation for this epidemiological finding is the association of infection with liver flukes (a kind of parasite) of the type *Optisthorchis viverrini* and possibly *Clonorchis sinensis* and the onset of cholangiocarcinoma of the intrahepatic bile ducts.[26] Liver flukes are common in South-Eastern Asia (particularly Thailand) inhabiting and laying eggs in the biliary system

inducing a chronic inflammatory state, presumably leading to malignant transformation of the lining epithelium.

The overriding link between most known risk factors and cholangiocellular carcinoma is chronic inflammation and chronic biliary irritation. From this point of view it has been suggested that HCV may also be a risk factor for the onset of cholangiocellular carcinoma. Indeed, recent studies provide convincing evidence that HCV infection is associated with the onset of cholangiocellular carcinoma. In patients with HCV infection the risk for onset of cholangiocellular carcinoma is increased (relative risk 2.6 (95% CI 1.5 to 4.6)).[23] The role of HCV in onset and pathogenesis of cholangiocellular carcinoma needs further investigation. Recent studies show that the HCV-core protein is significantly associated with cholangiocellular carcinoma invasion and metastasis.[27] The HCV-core protein can alter cellular proliferation and apoptosis in hilar cholangiocarcinoma cells. Because cholangiocellular carcinoma and hepatocellular carcinoma may arise from the same progenitor cells, common mechanisms may in part account for the malignant transformation.[28]

Non-Hodgkin's lymphoma and hepatitis C

There is a body of evidence indicating that infections play a role in the development of lymphomas as evidenced by the association of Ebstein-Barr virus infection with diffuse large cell B-NHL or *H. pylori* infection with mucosa-associated lymphoid tissue (MALT) lymphomas.[29,30] An association between HCV infection and lymphoproliferative disorders, such as MC or lymphoma has been reported by epidemiological studies recently published.[31,32] Between 50 and 90% of patients with MC (consisting of monoclonal immunoglobulins (Ig's), mostly IgM, combined with polyclonal Ig's with rheumatoid factor (RF) activity) have HCV infection; however, only 5% of patients with MC type 2 develop an overt B-cell malignancy.[33,34] In contrast, 5% of patients suffering from a B-cell NHL have evidence of HCV infection.[35] The relative risk for patients infected with HCV to develop B-cell NHL is increased showing a world wide geographic variation with the highest risk in southern Europe (relative risk 2.7).[36] HCV infections are commonly associated with diffuse marginal zone, follicular, large B-cell, and MALT lymphomas without any predilection for the HCV genotype.[37,38] In contrast, HCV-associated monoclonal gammopathy is more often seen in patients infected with either genotype 2a or 2b, respectively.[39]

The pathogenesis of HCV-induced lymphoproliferative disease is not entirely clear yet. Being a positive single-stranded RNA virus lacking a reverse transcriptase, it cannot cause direct insertional oncogenesis.[40] A leading concept suggests chronic antigenic stimulation leading to oligo- and monoclonal expansion of B-cells. In this concept, chronic HCV infection leads to an antigen-specific polyclonal B-cell proliferation. When the antigen is still present, partially transformed B-cell clones are further expanded leading first to oligoclonal and later to monoclonal B-cell proliferation as clinically evidenced by the presence of MC type III (polyclonal Ig's with RF activity) and MC type II, respectively.[40] Finally antigen-independent expansion leads to uncontrolled proliferation becoming apparent as B-cell lymphoma. The hypothesis is supported by the clinical finding that a significant decrease in the viral load by antiviral therapy results in a high percentage of complete response in both MC and B-cell lymphoma.[41,42] The variable regions of the Ig's in patients suffering from HCV infection with MC are hypermutated and the antibodies from different patients are related, as evidenced by variable (V_H)-gene restriction.[40] One of the antigens suspected to induce B-cell proliferation is HCV envelope protein E2. Since E2 can bind to CD81 on B cells, it may in complex with CD19 and CD22 provide strong co-stimulatory signals to support B-cell receptor activation. In addition, binding of E2 to CD81 induces double strand DNA breaks and hypermutations.[40] Besides chronic antigen stimulation, regulatory dysfunction of B cells, such as upregulation of FAS or overexpression of B-lymphocyte stimulator (BLyS), an important survival signal that may also serve as a co-stimulatory proliferation signal, may propagate B-cell expansion as well. Interestingly, patients with chronic HCV infection show a high rate of BCL-2 translocations and overexpression. In addition, patients with HCV infection with MC have a higher rate of BCL-2 expression as compared with HCV-infected patients without MC. However, it is important to realise that patients suffering from HCV infection can directly develop B-cell NHL without evidence of MC.[40] The above-presented concept of HCV-induced lymphoma may also hold true for hepatitis B as recent studies show that besides HCV, hepatitis B is also associated with the onset of lymphomas.[43,44]

CONCLUSION

Patients with chronic hepatitis C virus infection have an increased risk for development of at least three types of malignant disorders, in part probably due to the virus-induced stimulation of the immune system, inflammation and oxidative stress. Physicians should be aware of the HCV-associated onset of B-cell non-Hodgkin's lymphoma and cholangiocellular carcinoma besides hepatocellular carcinoma. This awareness is especially needed for detection of lymphoma when patients have mixed HCV-associated cryoglobulinaemia and incomprehensibly high LDH serum levels as illustrated by the case presented.

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REVIEW

Treatment extension benefits HCV genotype 1 patients without rapid virological response: a systematic review

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ABSTRACT

Background: Current guidelines recommend 48 weeks of treatment with pegylated interferon and ribavirin for patients infected with chronic hepatitis C virus (HCV) genotype 1. Several clinical trials have investigated the efficacy of treatment duration longer than 48 weeks, but yielded discordant results.

Methods: We performed a structured search of PubMed, Web of Science and the Cochrane library to identify randomised clinical trials in HCV genotype 1 patients who were treated either for 48 or 72 weeks. Sustained viral response (SVR) data were pooled and a sample size weighted pooled proportion was calculated.

Results: We identified five studies matching our criteria. Studies randomised at baseline (n=1), at absence of rapid virological response (RVR) at week 4 (n=1), at early virological response at week 12 (EVR) (n=1) or at slow response at week 24 (n=2). In the RCT that randomised at absence of RVR, SVR was significantly higher in the extended treatment arm (57 *vs* 42%, p=0.02) with an RR of 1.35 (95% CI 1.04 to 1.75). This tendency was also observed in the studies that randomised at slow response (44 *vs* 35%), although no longer statistically significantly different.

Conclusion: Prolonged 72-week treatment should be considered in HCV genotype 1 patients without RVR at week 4, as this increased SVR.

KEYWORDS

Hepatitis C, systematic review, antiviral therapy, treatment duration

INTRODUCTION

Infection with hepatitis C virus (HCV) is a significant cause of chronic liver disease.[1] It has been estimated that approximately 170 million people, 3% of the world's population, suffer from HCV infection and it is one of the main causes of chronic liver disease and indication for liver transplantation in the United States and in Europe.[2] Six distinct but related HCV genotypes and multiple subtypes have been identified on the basis of molecular resemblance, of which genotype 1 is most common in the US and Western Europe.[2] The probability of eradicating HCV depends on the genotype; and current treatments give better responses for genotypes 2 and 3, as compared with genotypes 1 and 4.[3,4]

The currently recommended treatment for patients infected with HCV genotype 1 is pegylated interferon (PEG-IFN), in combination with weight-based 800 to 1400 mg ribavirin daily, for 48 weeks.[5] Approximately 40 to 60% of patients achieve a sustained virological response (SVR) with this regimen.[3,4,6] The efficacy of treatment against HCV has improved, but is still far from ideal. It remains complex, is costly and has substantial side effects, which often lead to early discontinuation and consequent treatment failure.

This has led to the introduction of tailor-made therapy, a dynamic approach that individualises treatment on the basis of measurement of HCV viral load at given time points. In HCV genotype 1, patients with low viral load at onset and undetectable HCV RNA after four weeks of treatment (rapid virological response, RVR), 24 weeks of treatment is equally effective as standard 48 weeks.[7] For patients without RVR and with undetectable HCV RNA after 24 weeks of treatment, the situation is less clear.

The SVR rates in these patients are lower compared with the patients with RVR, even with treatment duration of 48 weeks. This has led to the hypothesis that longer treatment of up to 72 weeks may cure slow-responding HCV patients.

Recently, some clinical trials have investigated the efficacy of extending treatment duration to 72 weeks, but yielded discordant results.[8-12] Two prospective studies found significantly higher SVR rates with prolonged treatment compared with standard 48 weeks in HCV genotype 1 patients.[11,12] In contrast, three other trials have demonstrated that extending duration of treatment does not result in better SVR rates.[8-10] A systematic analysis of the data from these individual trials is necessary to address the issue and judge whether longer treatment indeed increases efficacy and which patients benefit from extended treatment.

The purpose of this systematic review is to evaluate different treatment duration regimes on achieving SVR and to make an evidence-based recommendation on the optimal length of treatment for HCV genotype 1 patients.

METHODS

Literature search

We followed the QUORUM guidelines for all steps reported in this systematic review.[13] A systematic literature search with predefined search terms was carried out in Medline (PubMed), Cochrane CENTRAL, Web of Science® and ClinicalTrials.gov for articles and abstracts published from 2000 until March 1, 2010.

The keywords 'HCV or hepatitis C', 'ribavirin or Rebetol® or Copegus®' and 'pegylated interferon, peginterferon, Pegintron® or Pegasys®' were combined. We used the following search limits: human; adults; randomised clinical trials; and English language.

Study selection

We selected prospective studies that evaluated standard pegylated interferon and ribavirin combination therapy in HCV genotype 1 patients and randomly compared extended (72 weeks) with standard (48 weeks) treatment duration. We adopted the following inclusion criteria: manuscripts written in English, adults (+18 years) with chronic HCV genotype 1, use of standard combination therapy similar in both arms, randomised controlled trials, availability of SVR rates in both arms, and the report was published in a book, journal, proceeding or indexed abstraction.

Exclusion criteria were studies referring to patients with HIV co-infection, hepatitis B virus co-infection, decompensated liver cirrhosis, hepatocellular carcinoma, haemophilia, and liver or renal transplantation. Studies that involved previously treated patients, relapsers or patients unresponsive to previous treatment were also excluded.

An additional search was performed using references of all included articles to retrieve eligible studies possibly missed by our systematic literature search.

Validity assessment

The quality of the randomised controlled trials (RCTs) was assessed and scored using the Jadad scale, which considers three items: randomisation (1 point if yes or 2 points if the method to generate the sequence of randomisation was described and appropriate), double blinding (1 point if yes or 2 points if the method of double blinding was described and appropriate) and description of withdrawals and dropouts (1 point).[14]

Data abstraction

Titles and abstracts of all retrieved records and subsequently full-text articles were examined independently by two investigators (TG and SS) to identify RCTs that satisfied the inclusion criteria. Discrepancies in selection were resolved by discussion between the authors of this systematic review.

All data from the selected studies were extracted using a standardised data collection form. The following characteristics were recorded: year of publication, study design, funding by pharmaceutical company, full text and population baseline characteristics (age, gender, body mass index, HCV viral load, fibrosis stage and ethnicity).

Data were separated and extracted for extended and standard treatment regarding the following: randomisation time point, number of participants per treatment arm, duration of treatment, dosages and type of pegylated interferon and ribavirin, end of treatment (EOT) and SVR.

Endpoints of interest

The primary outcome of interest in this systematic review was to explore SVR rates; we used the following definition: a negative result on a qualitative PCR assay for HCV RNA 24 weeks after the EOT. The secondary endpoint was EOT, defined as a negative result on a qualitative PCR assay for HCV RNA after termination of treatment (extended 72 weeks *vs* standard 48 weeks).

Statistical analyses

The effect of the two management strategies on SVR rates in HCV genotype 1 patients was expressed as a relative risk (RR) with a 95% confidence interval (CI) using the Mantel-Haenzel method. If possible, a sample size weighted pooled proportion and a pooled RR were calculated after data on SVR were pooled. The number needed to treat is calculated as 1 divided by the absolute risk reduction. Outcomes were analysed on an intention-to-treat basis. All data were pooled using a random effect

model, and statistical analyses were performed using Review Manager version 5.0.24 for Windows (provided by the Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Trial characteristics

We identified five potential RCTs matching our criteria, representing a total of 1267 HCV genotype 1 patients. All RCTs were published as full papers.[8-12] The selection of articles is depicted in *figure 1*. Maximal quality for the RCTs in this systematic review was a Jadad score of 3 points. All studies were open-label RCTs and described their dropouts and withdrawals.

The included studies differed in time of randomisation. We identified RCTs that randomised at baseline,[8] at absence of RVR at week 4,[12] at early virological response (EVR) at week 12 [10] or at slow response at week 24.[9,11] Detectable HCV RNA levels at week 4 and an undetectable HCV RNA at week 12 or a ≥2 log10 decrease from baseline serum HCV RNA was defined as an EVR. A slow responder was defined as a patient with at least a 2-log10 decrease in baseline serum HCV RNA at week 12 and undetectable serum HCV RNA at week 24. All non-responders at week 24 were excluded from analysis. Characteristics of the five studies and corresponding study populations are given in *table 1*. While the baseline characteristics of two studies also include data from patients with genotype 2, 3 or 4,[10,12] the majority of these populations comprised genotype 1 patients (>90%).

In two studies, the treatment regimen consisted of ribavirin and pegylated interferon-α2b of 1.5 μg/kg/week,[9,11] while in three studies pegylated interferon-α2a was administered at 180 μg/week.[8,10,12] In one study, patients assigned to the extended treatment group received a lower dose of pegylated interferon-α2a after week 48 (135 μg/week).[10] Ribavirin was given at a fixed dose of 800 mg daily in two trials [8,12] and at a body weight-based dosage of 800 to 1400 mg daily in three trials.[9-11]

Analysis of SVR rates

In the study that randomised at 4 weeks, patients without a virological response after 24 weeks of treatment were also included.[12] Therefore, non-responders (detectable serum HCV-RNA level at 24 weeks with a <2 log10 decrease from baseline) were excluded and a subgroup analysis was performed on 242 patients comparing extended (72 weeks) with standard (48 weeks) treatment duration *(figure 2)*. This study population also included patients with other genotypes; however, the majority of these patients were genotype 1 (˜ 90 %). The other trials all included exclusively genotype 1 patients. In the study by Sánchez-Tapias, SVR was significantly higher with

Figure 1. *Selection of articles*

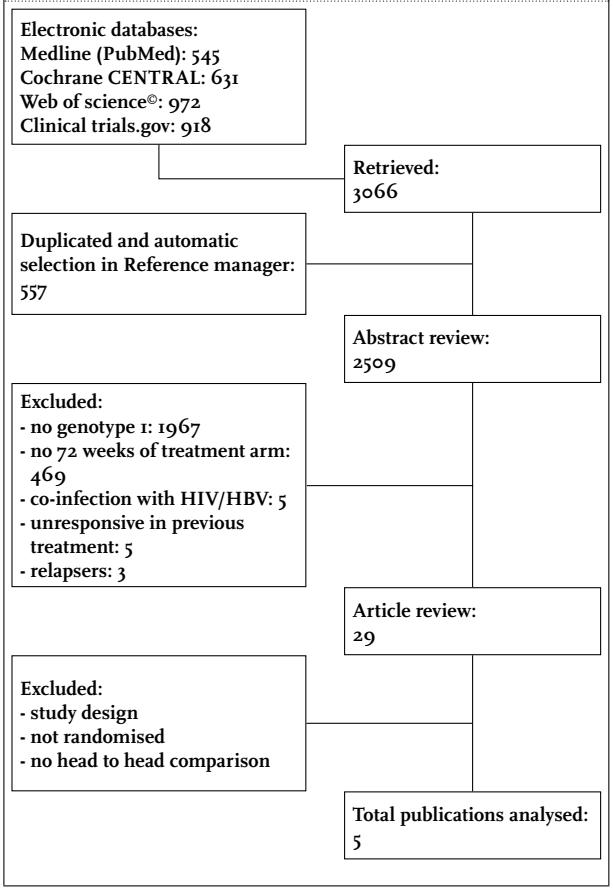
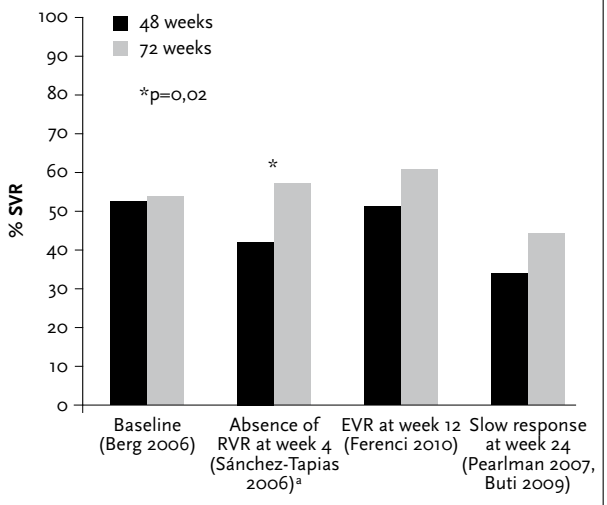


Figure 2. *SVR rates after standard versus extended HCV combination therapy of trials randomised at different time points*



[a]**Results of subgroup analysis with non-responders at 24 weeks of treatment excluded.**

Table 1. *Characteristics of the randomised controlled trials used in the systematic review of therapies on HCV genotype 1 patients*

Study	Patients, n	Randomisation	Industry funded	Jadad scale	PEG IFN	Ribavirin, mg	Mean age, years (±SD)	Male gender, n (%)	Mean BMI, kg/m² (±SD)	HCV viral load, x 10^6 IU/ml, mean (±SD)	Fibrosis/ cirrhosis Metavir score, n (%)	Ethnicity
Berg[8]	455	Baseline	yes	3	α2a	800	42.7 (11.4)	250 (54.9)	25.5 (4.2)	5.77 (0.52)	F3-4: 36 (8)	Caucasian
Sánchez-Tapias[12]	291	Absence of RVR	yes	3	α2a	800	43.0[a]	215 (66)[a]	24.7[a]	1.04[a]	NA	Caucasian
Ferenci[10]	261	EVR	yes	3	α2a	1000-1200	44.7[a]	188 (65)[a]	NA	0.67[a,b]	F3-4: 57 (20)[a]	Caucasian
Pearlman[11]	101	Slow response	no	3	α2b	800-1400	55 (25-66)[c]	67 (66)	28.9	5.3	F3-4: 26 (26)	Mixed
Buti[9]	159	Slow response	NA	3	α2b	800-1400	45.4 (10.7)	98 (61.6)	NA	6.59	NA	Caucasian

[a]Includes data of patients with other genotypes; [b]median; [c]mean (range). RVR = rapid virological response; EVR = early virological response; PEG-IFN = pegylated interferon; BMI = body mass index; HCV = hepatitis C virus; NA = not applicable.

72 weeks (57%) compared with the standard treatment (42%, p=0.02) with an RR of 1.35 (95% CI 1.04-1.75) and a number needed to treat (NNT) of 7 *(table 2)*.[12]

In the study that randomised at baseline,[8] no statistically significant difference was found for SVR rates at 48 (SVR 53%) or 72 weeks (SVR 54%) *(figure 2)*. In the study that randomised at EVR, higher SVR rates were observed with extended treatment when compared with standard treatment,[10] although the observed difference was not statistically significant (60 *vs* 51%).

One trial with a total of 101 patients randomised at slow response favoured longer (72 weeks, SVR 38%) treatment over standard (48 weeks, SVR 18%, p=0.026) treatment.[11] In contrast, a second trial studying 159 slow responders showed no statistically significant difference on effect of extended (48%) *vs* standard (43%) treatment.[9] We found a sample size weighted pooled proportion of 44% for 72 weeks and 35% for 48 weeks, corresponding with a pooled RR of 1.42 (95% CI 0.77 to 2.63) *(table 2)*.

Table 2. *Relative risks of SVR rates after standard versus extended HCV combination therapy of trials randomised at different time points*

Time point of randomisation	Study	RR (pooled)	95% CI
Baseline	Berg[8]	1.02	0.86-1.21
Absence of RVR	Sánchez-Tapias[12]	1.35	1.04-1.75[a]
EVR	Ferenci[10]	1.18	0.95-1.47
Slow response	Pearlman, Buti[9,11]	1.42	0.77-2.63

RR = relative risk; CI = confidence interval; RVR = rapid virological response; EVR = early virological response; [a]P = 0.02, standard treatment *vs* extended treatment.

Analysis of EOT rates

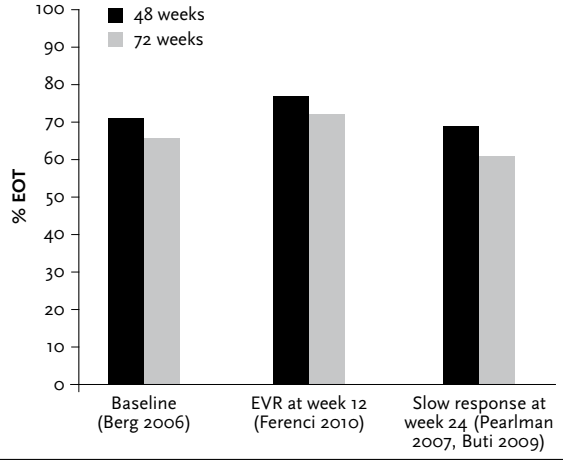
The EOT rates of the standard *vs* the extended treatment group were comparable in all trials *(figure 3)*. Slightly higher EOT rates were seen in the standard treatment group in the studies that randomised at baseline (71 *vs* 66%), at EVR (76 *vs* 72%) and at slow response (69 *vs* 61%).[8-11] No EOT rates were calculated in the subgroup analysis in the study by Sánchez-Tapias et al.[12] None of the observed differences were statistically significant.

All trials showed similar withdrawal rates related to serious adverse events among treatment arms.

DISCUSSION

The key finding of our systematic review is that HCV genotype 1 patients without RVR at week 4 may benefit

Figure 3. *EOT rates after standard versus extended HCV combination therapy of trials randomised at different time points*



from an extended combination therapy of 72 weeks. Furthermore, 72 weeks of combination treatment led to higher SVR rates in trials that randomised at baseline, at 12 weeks or at 24 weeks, although the difference was no longer statistically significant. For the latter studies, EOT rates were comparable in both arms. This suggests that the differences in SVR likely result from the proportion of patients who relapsed after the standard 48 weeks of treatment.

Due to the systematic design of our literature search with predefined inclusion and exclusion criteria, we only included randomised clinical trials that compared head-to-head standard *vs* prolonged treatment. Two interesting RCTs did not meet the inclusion criteria of our systematic review, as the length of the extended treatment in these trials was variable.[15,16] Patients in these studies received individualised treatment based on the time when HCV RNA first became undetectable instead of fixed treatment duration of 72 weeks and were not randomised in the variable treatment group. Nonetheless, our results are generally in line with the study by Mangia *et al.*[16] In a subgroup analysis of patients with EVR at week 12, substantially higher SVR rates were attained if the patient was treated for 72 weeks (63 *vs* 38%,), although this difference was not statistically significant (p=0.068). In the same line, these results were also found in the trial by Ferenci *et al.*, that randomised at EVR (60 *vs* 51%).[10] In this study, patients were included with both complete and partial EVR (detectable HCV RNA at weeks 4 and 12, with a ≥ 2-log10 decrease from baseline in serum HCV RNA at week 12), while the study by Mangia *et al.* only included patients with complete EVR. Patients with complete EVR have a higher probability of achieving an SVR than patients with partial EVR; therefore, we would expect lower SVR rates in the study by Ferenci *et al.*[17] However, the low number of patients in the subgroup analysis by Mangia *et al.* precludes definite conclusions.

Ide *et al.* showed that extending treatment by 44 weeks once HCV RNA levels first became undetectable significantly increased SVR rates in patients who were HCV RNA negative at 16 to 24 weeks.[15] This is in contrast with our results, because we did not find a benefit in extending treatment for patients with undetectable HCV RNA levels after week 12 (slow responders). Another finding in the study by Ide and colleagues was that patients with undetectable virus at week 8 and 12 had similar SVR rates in both treatment groups. This observation is consistent with our results; patients with an EVR at week 12 do not benefit from extended treatment.[10] Nevertheless, no definite conclusions about the value of this strategy can be drawn from this study due to small sample sizes.

In our systematic review, two trials were included that used a fixed dose of ribavirin of 800 mg/day instead of weight-based dosage regimens (800 to 1400 mg daily).[8,12] A previous study showed that low fixed dose of ribavirin (800 mg/day) was inferior to a higher weight-based dose of ribavirin (1000 or 1200 mg/day) regarding attaining SVR rates when treated for standard 48 weeks.[18] However, the optimal ribavirin dosage regimen for 72 weeks of treatment has not yet been elucidated. It is possible that suboptimal dosage of ribavirin in this study might have impacted more negatively on SVR rates when treated for 48 weeks of treatment than for the extended 72 weeks.[12] However, another RCT also used a suboptimal dose of ribavirin (800 mg/day) and did not find this difference in SVR rates.[8] The observed difference in SVR rates between these two trials could be caused by the mixture of rapid and slow virological responders in one trial.[8] We found similar SVR rates among trials that used weight-based dosages.[9-11]

In the included trials, two types of pegylated interferon (α2a and α2b) were investigated in combination with ribavirin. Current evidence suggests that peginterferon α2a is associated with higher SVR than peginterferon α2b.[19] Both trials that randomised at slow response used pegylated interferon α2b, while the other trials used pegylated interferon α2a. The results of trials using pegylated interferon α2a cannot be extrapolated to patients using pegylated interferon α2b and vice versa, due to these differences in pharmacokinetic profiles. Furthermore, in one study a lower dose of pegylated interferon-α2a was given after week 48 (135 μg/week). This suboptimal dose of pegylated interferon may lead to lower SVR rates, although this has not been formally proven in randomised clinical trials. [10]

One study did not require patients with detectable HCV RNA at week 24 to discontinue further treatment.[12] According to protocol, patients with detectable HCV RNA at 24 weeks are regarded as non-responders and should therefore be excluded from further treatment.[5] This study also performed a subgroup analysis on patients with an undetectable serum HCV RNA level or a ≥2 log10 decrease from baseline in serum HCV RNA levels at 24 weeks of treatment, thereby excluding the non-responders. Ten percent of this study population consisted of patients with genotype 2, 3 or 4. It is possible that the observed difference in SVR rates between 48 and 72 weeks of treatment could be explained by the proportion of patients with genotype 2 and 3, patients known to have better treatment responses, in both treatment groups. However, due to the low proportion of patients with genotype 2 and 3, eight in the standard treatment group and nine in the extended treatment group, respectively, this effect is negligible.

The main strength of our study is that we systematically analysed all RCTs that compare duration of therapy in HCV genotype 1 patients. Although included RCTs use different times of randomisation, we provide an overview

for clinicians faced with the difficult decision-making in treating patients with HCV genotype 1. Another strength of this systematic review was that all included trials had a sizeable number of genotype 1 patients and that the number of patients were comparable in all studies. Our systematic review comes with some limitations. First, this systematic review only focuses on timing of viral response as a key success factor. We know that genetic variants of IL-28B are strongly associated with the response to HCV treatment. Indeed, the beneficial (CC) IL-28B genotype is associated with improved early viral kinetics and greater likelihood of RVR, complete EVR, and SVR.[20] Secondly, because of the heterogeneity in study design of the included trials, we were unable to analyse potentially important predictors of outcomes such as race, severity of baseline disease and body mass index due to inaccessibility of individual patient data.

Our study provides important information for clinicians treating HCV genotype 1 patients. Absence of RVR at week 4 is an important parameter in determining the success of extending treatment to 72 weeks. Although abbreviated regimens have tolerability advantages, are less expensive and reduce exposure to side effects, less relapse occurs with prolonged treatment. Furthermore, extending treatment does not lead to higher withdrawal rates due to serious adverse events. If compliance of patients assigned to 72 weeks can be improved, the probability of attaining SVR rates can be further maximised. On the other hand, patients assigned to 72 weeks of treatment have higher dropout rates compared with patients in standard treatment groups and are less likely to be cured, thereby possibly increasing costs. Furthermore, if all non-RVR patients are treated for 72 weeks, costs of treatment will increase. Therefore, even if extending treatment duration to 72 weeks should yield better SVR rates, it still needs to be determined whether this prolongation is cost-effective.

In conclusion, this systematic review demonstrates that in HCV genotype 1 patients without RVR at week 4, treatment extension with pegylated interferon and ribavirin to 72 weeks increased SVR significantly. However, the consequence for current daily practice is unclear as the ribavirin dosage now used is higher and the optimal ribavirin dose for 72 weeks of treatment has not been determined yet. Furthermore, in slow responders the standard duration of treatment should still be 48 weeks, although a beneficial effect of 72 weeks of combination treatment could not be excluded. Prolonging treatment duration to 72 weeks might be considered in HCV genotype 1 patients who do not reach RVR at week 4.

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PHOTO QUIZ

Episodes of abdominal pain

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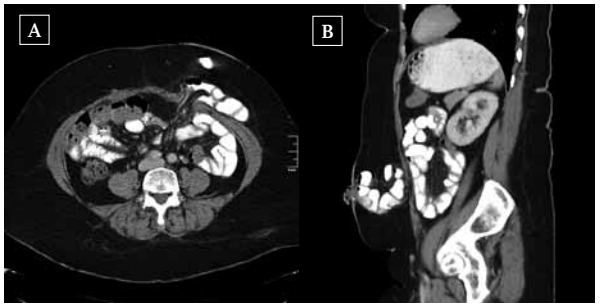
CASE REPORT

A 63-year-old lady presented with abdominal pain after an abdominal perineal rectum amputation (APR) combined with an end colostomy for a T3N1 adenocarcinoma, in 2008.

In the last year, she had undergone 15 episodes of abdominal pain similar to the current presentation, resulting in many visits to different hospitals, some leading to admission. During analysis, several X-rays showed signs of an ileus. However, no cause could be identified in any of the presentations and the patient recovered spontaneously.

During her last admission, she presented with pain in the epigastric region which had persisted for the last 24 hours and radiated to the umbilicus. Simultaneously stoma production stopped, despite using Movicolon four times a day on a regular basis. Physical examination revealed no abnormalities, besides obesity. The stoma looked vital and digital examination showed no abnormalities. As contrast colography showed a stenosis at 15 cm oral to the stoma, a colonoscopy was performed, showing no abnormalities.

Figure 1.



Again, the patient recovered uneventfully and a CT was ordered as part of her follow-up (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 228 for the answer to this photo quiz.

Netherlands
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PHOTO QUIZ

H1N1 vaccination: expect the unexpected

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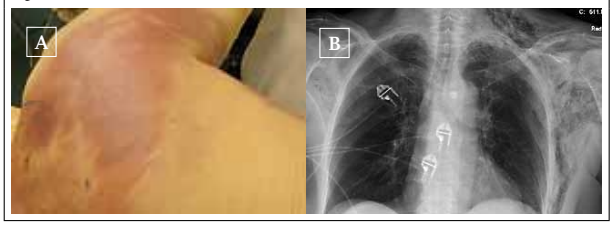
CASE REPORT

A 71-year-old woman presented to the emergency department of our hospital, three days after receiving the H1N1 influenza vaccine. She started feeling unwell one day after receiving the vaccine in her left forearm, complaining of abdominal pain and nausea (without vomiting). On the day of presentation she developed fever, rapidly progressive pain in the left shoulder and blurred speech. Further history revealed a depressive disorder and oesophageal stenosis as a result of corrosive ingestion. Her medication comprised only lithium and pantoprazole. At presentation in the emergency room, we saw a severely ill patient with a blood pressure of 100/70 mmHg, a pulse rate of 120 beats/min and a temperature of 38.2 °C. The patient was in severe respiratory distress. Although the physical examination of her left shoulder region by her general practitioner, two hours before presentation was unremarkable, we observed oedematous, discoloured skin and crepitus, extending from the left shoulder *(figure 1A)*. Laboratory analysis revealed a procalcitonin of 52.7 ng/ml and a C-reactive protein of 305 mg/l. Chest X-ray showed extensive subcutaneous emphysema *(figure 1B)*.

Figure 1. *[A] A bleu line is marking the edge of skin lesions at presentation. These skin lesions are on the contralateral side of the initial left shoulder lesion. [B] Chest X-ray revealing subcutaneous emphysema at the left shoulder site.*



WHAT IS YOUR DIAGNOSIS?

See page 246 for the answer to this photo quiz.

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REVIEW

Illness-induced changes in thyroid hormone metabolism: focus on the tissue level

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ABSTRACT

During illness changes in thyroid hormone metabolism occur, collectively known as the non-thyroidal illness syndrome (NTIS). NTIS is characterised by low serum thyroid hormone levels without the expected rise in serum thyroid-stimulating hormone, indicating a major change in thyroid hormone feedback regulation. Recent studies have made clear that during NTIS differential changes in thyroid hormone metabolism occur in various tissues, the net effect of which may be either activation or inhibition of thyroid hormone action. In this review we discuss systemic and local changes in thyroid hormone metabolism during illness, highlighting their physiological implications in terms of disease course.

KEYWORDS

Deiodinase, inflammation, non-thyroidal illness syndrome, thyroid hormone

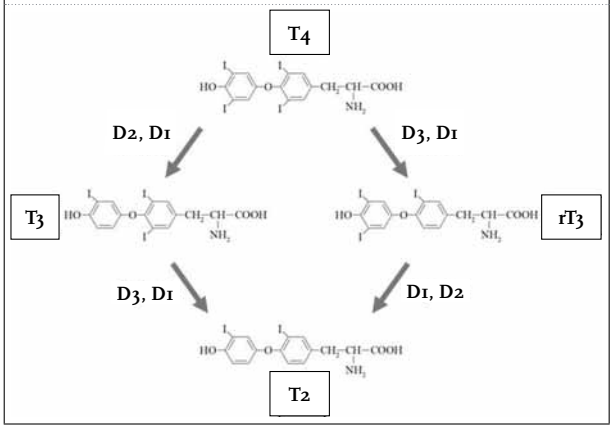
THYROID HORMONE METABOLISM

Thyroid hormones play a key role in energy homeostasis in adult life. The setpoint for thyroid hormone production and secretion by the thyroid gland is regulated by the hypothalamic neuropeptide thyrotropin-releasing hormone (TRH), determining the balance between serum thyroid-stimulating hormone (TSH) and thyroid hormone (TH) concentrations.[1] The major form of TH produced by the thyroid is the inactive prohormone thyroxine (T_4).[2] T_4 can be converted into the biologically active tri-iodothyronine (T_3) by the removal of an iodide by the selenoenzyme family of iodothyronine deiodinases, which have a tissue-specific distribution. There are three deiodinases, i.e., type 1 (D1), type 2 (D2) and type 3 (D3).[3] Both the inner (phenolic) ring and the outer (tyrosyl) ring of T_4 can be deiodinated, ultimately leading to the formation of 3,3'-di-iodothyronine (T_2) *(figure 1)*.

NON-THYROIDAL ILLNESS SYNDROME

During illness many aspects of thyroid hormone metabolism change, collectively known as the non-thyroidal illness syndrome (NTIS). The hallmark of NTIS is decreased serum thyroid hormone levels without an increase in TSH and TRH expression, indicating the absence of negative feedback regulation. This may represent a useful adaptation of the body to counteract excessive catabolism observed during illness and can be viewed as a part of the acute phase response.[4] However, especially during prolonged critical illness in the ICU setting NTIS may be maladaptative.[5]

Figure 1. *Overview of the deiodination of thyroxine (T_4) into tri-iodothyronine (T_3), reverse tri-iodothyronine (rT_3) and di-iodothyronine (T_2), showing the role of the various deiodinase subtypes*



In the last decade several rodent models of NTIS have been established to unravel the mechanisms behind NTIS. For instance, acute inflammation can be induced in rats and mice by the administration of the bacterial endotoxin lipopolysaccharide (LPS), resulting in decreased serum T_3, T_4 and TSH within 24 hours.[6,7] Chronic inflammation can be induced by a turpentine injection in the hindlimb of mice inducing a local sterile abscess and a decrease in serum T_3 and T_4 within two days.[8] Finally, *S. pneumoniae* infection, inducing severe bronchopneumonia and septicaemia in rats, reduces serum T_3 and T_4 significantly in relation to the extent of bacterial outgrowth in the lung and spleen.[9] An animal model of prolonged critical illness was developed in Leuven, using parenterally fed rabbits with a burn injury, displaying decreased serum T_3 and a tendency to decreased serum T_4.[10] Recent work has shown that illness-induced alterations in serum T_4, T_3 and TSH levels are accompanied by significant and highly diverse changes in deiodinase expressions in a variety of tissues and organs of patients and experimental animals.

ILLNESS-INDUCED CHANGES IN DEIODINASE EXPRESSION

The changes in central hypothalamic thyroid hormone metabolism reported during illness are remarkably similar in all animal models studied. Generally, D2 expression increases[6,11-14] while D3 expression decreases.[15] The net result is probably increased local bioavailability of T_3, which may help to prevent the activation of hypophysiotropic TRH neurons in the hypothalamus and to persistently suppress the hypothalamic-pituitary-thyroid axis at the central level.[16-18] In contrast to hypothalamic D2, pituitary D2 expression varies during illness, depending on the genetic background as well as type of illness.[6,12,15]

In the liver of all NTIS models D1 decreases, while liver D3 varies depending on the type of illness.[8-10,19,20] This discrepancy is currently under investigation and might be explained by differences in feeding status.

In muscle, D2 expression decreases while D3 increases in septic patients and in mice infected with *S. pneumoniae*.[21,22] In contrast, muscle D2 expression appeared to be increased in post-mortem muscle biopsies of prolonged critically ill patients[23] and in muscle of mice with acute inflammation, the latter in association with decreased D3.[20] Finally, in mice with local chronic inflammation, both muscle D2 and D3 increase simultaneously.[22] In sum, changes in pituitary, liver and muscle deiodinase expression are dependent on type and severity of illness and possibly also on species/genetic background studied. Infiltrating granulocytes in the turpentine-induced abscess showed a marked induction of D3.[8] This phenomenon was subsequently confirmed in animal models of bacterial pneumonia and peritonitis.[9]

SYSTEMIC CONSEQUENCES OF CHANGED DEIODINASE EXPRESSION

Yu and Koenig showed in an LPS model that restoration of liver D1 expression by exogenous administration of the steroid receptor co-activator (SRC)-1 prevents the development of low serum T_3, pointing to liver D1 as the key contributor to decreased serum T_3 levels in rodents.[24] In contrast, during prolonged illness the decrease in liver D1 appeared to result from decreased T_3 levels, as infusion of T_4 and T_3 abolished the liver D1 decrease.[25] Our group reported that the decrease in serum T_3 preceded the LPS-induced decrease in liver D1, but we observed the reverse order using a slightly higher dose of LPS.[6,26]

The possible role of D2 in the lowering of serum TH levels during NTIS is controversial as well. Although decreased D2 expression in skeletal muscle has been proposed to contribute to decreased serum TH, most studies reported increased muscle D2 while serum TH levels decreased.[22,23,26]

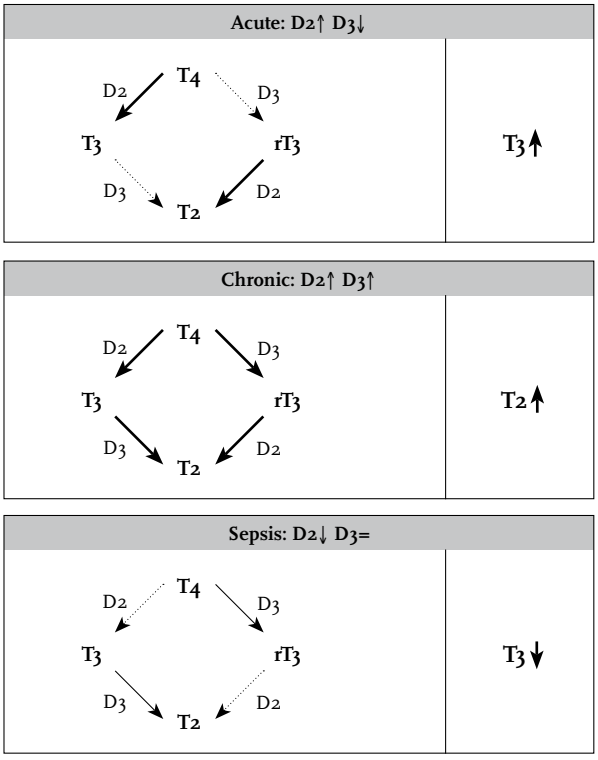
Finally, D3 induction has been considered a possible contributor to decreased serum T_3 and increased rT_3 levels during prolonged critical illness in humans.[19] However, animal studies do not support this as abundant local D3 expression in our chronic inflammation model is not sufficient to decrease serum T_3 levels[8] and mice devoid of D3 show a similar decrease of serum TH levels during bacterial pneumonia compared with wild-type mice.[13]

Consumptive hypothyroidism has been described in massive infantile haemangiomas, which is likely due to the high expression of D3 in haemangioma cells.[27] Since the expression level of D3 in haemangioma cells is much higher than in liver during illness, this intriguing disease entity does not present strong support for a role of D3 in decreasing serum T_3 levels during NTIS. Animal studies do not point to a clear-cut role for D1, D2 and D3 in illness-induced alterations in serum thyroid hormone concentrations during illness. However, it should be kept in mind that the contribution of the thyroid gland to serum T_3 production differs between humans and rodents (~20% in humans *vs* ~50% in rodents), leaving open the possibility of a more prominent role for the deiodinases in humans compared with rodents. Moreover, deiodinase knock-out mice display normal serum T_3 levels indicating that a decrease in peripheral T_3 production by deiodinases during illness cannot be solely responsible for the decrease in serum T_3 observed during illness.

LOCAL CONSEQUENCES OF CHANGED DEIODINASE EXPRESSION

It is now clear that the illness-induced decrease of serum T_3 and T_4 is associated with heterogeneous changes in

Figure 2. *Schematic representation of the differential alterations in muscle deiodinase expression in mouse models of illness: acute inflammation (LPS administration, upper panel), chronic inflammation (turpentine induced abscess, middle panel) and severe bacterial infection and sepsis (S.pneumoniae infection, lower panel)*



On the left side the observed alterations in deiodinase expression, on the right side the theoretical net result in terms of local T_3 and T_2 concentrations.

peripheral thyroid hormone metabolism. In addition, the peripheral changes are not the key determinants of decreased serum T_3 and T_4 levels. These observations suggested an alternative role of deiodinase changes during illness. It seems obvious that tissue deiodinase activities are important determinants of local T_3 generation. This was most clearly demonstrated in the hypothalamus, where increased D2 and decreased D3 activities result in decreased local T_3 availability and, thereby, suppression of TRH expression in the paraventricular nucleus.[16,17] This paracrine loop was recently supported by an elegant *in vitro* study.[28]

In liver, the changes in deiodinase expression during NTIS might result in net decreased hepatic T_3 concentrations. This may be beneficial as food intake usually decreases dramatically during illness and many T_3-regulated genes in the liver are involved in energy metabolism. However, there are no experimental studies to date to support this notion. Muscle deiodinase expression also changes profoundly, depending on the type and severity of illness. The differential regulation of muscle D2 and D3 expression are likely to result in different outcomes in terms of T_3 and T_2 muscle concentrations in the different mouse models of illness. This is depicted schematically in *figure 2*. Both T_3 and T_2 are known to regulate muscle metabolic state.[29,30] It is, therefore, tempting to speculate that differential regulation of deiodinase expression contributes to alterations in muscle metabolic state during the different stages of disease. During sepsis, mitochondrial dysfunction is frequently observed.[31] As both T_3 and T_2 are important in mitochondrial biogenesis and activity,[29,30] a tissue-specific shortage of T_3 and/or T_2 may contribute to sepsis-induced mitochondrial dysfunction. Furthermore, as thyroid hormone is an important regulator of type and contractibility of muscle fibres,[32] changes in muscle deiodinase expression might contribute to critical illness myopathy (CIM), which is frequently observed in ICU patients.[33]

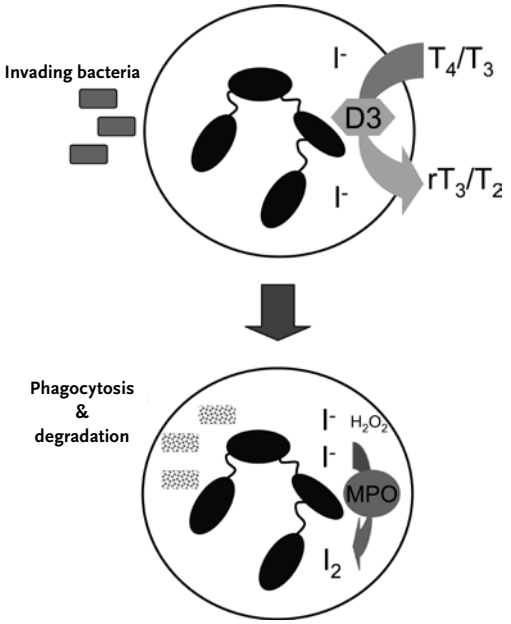
BACTERIAL KILLING

The possible function of D3 expression in activated granulocytes is intriguing. TH plays a role in differentiation and proliferation of cells with high T_3 inducing cell differentiation and low T_3 inducing cell proliferation. Granulocytes are short-living, fully differentiated cells that migrate to the site of infection and do not proliferate, which may argue against a role for D3 induction in differentiation or proliferation of activated granulocytes. Studies from the 1960s already suggested a role for thyroid hormone in the bacterial killing capacity of leukocytes. One of the major antibacterial mechanisms is the myeloperoxidase system, which exerts its antimicrobial effect in combination with hydrogen peroxide (H_2O_2) and a halide such as iodide. Thyroid hormones are an important source of iodide, and it was shown in 1964 that leukocytes take up and deiodinate T_4, thereby generating inorganic iodide.[34] In combination with the recent demonstration of D3 induction in infiltrating leukocytes during infection, it is tempting to speculate that D3 induction helps to generate iodide as part of the innate immune response *(figure 3)*. Studies in *S. pneumoniae*-infected D3KO mice indeed showed a defective bacterial clearance compared with wild-type mice, which supports this hypothesis.[13]

CONCLUDING REMARKS

Current knowledge has completely altered the concept of NTIS. In the classic view, NTIS is a syndrome with low plasma TH concentrations as its key phenomenon. Recent studies, however, have clearly shown that NTIS represents a profound and differential change in thyroid

Figure 3. *Proposed model of the contribution of granulocyte D3 expression to bacterial killing*



Upper part: generation of iodide by deiodination of T_4 and T_3. Iodide needs to be oxidised into iodine (I2) in order to become biologically active in the defence against bacteria. This is represented in the lower part, showing the generation of iodine by MPO leading to bacterial killing.

hormone physiology at the organ level in terms of local TH metabolism. Changes in tissue deiodinase expression should be interpreted in the context of type of illness and of the organ/tissue studied. Finally, the granulocyte is proposed as a novel and important cell type involved in NTIS during bacterial infection.

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ANSWER TO PHOTO QUIZ (PAGE 222)

EPISODES OF ABDOMINAL PAIN

DIAGNOSIS

The scan revealed a parastomal hernia including small bowel loops. Parastomal hernia is a common late complication of end colostomy, with an incidence up to 50%, depending on stoma type and length of follow-up.[1] Most parastomal hernias are asymptomatic, although many patients experience discomfort or pain and intermittent episodes of obstruction. In addition, even severe life-threatening complications can occur such as strangulation, perforation and total obstruction.

Often, these hernias are caused by surgical-related problems, such as the use of a trephine that is too large, or formation outside the rectal muscle. Nontechnical factors are thought to be the same as with other abdominal hernias, including obesity and waist circumference,[2] malnutrition, high intra-abdominal pressure, corticosteroid use, malignancy, increasing age and postoperative wound infection.[1]

Clinical demonstration is not always obvious, and therefore Valsalva manoeuvre and supine position can help to reveal the hernia. As physical examination may be difficult, especially in obese patients, imaging is justified in patients with a high index of suspicion. Both CT scan and ultrasonography can be helpful, although thorough physical examination accompanied by imaging seems to provide the most accurate results.[3]

Most parastomal hernias are treated conservatively, with or without a stomal supporting device. Intervention is necessary in case of obstruction or strangulation. As local primary repair or relocation have demonstrated even higher recurrence rates compared with primary stoma formation,[1] research has focused on the use of mesh repair, showing better results.[4] As a consequence, in the prevention of parastomal hernia, some suggest using the mesh technique in primary stoma formation.

In patients with a stoma and abdominal pain, a parastomal hernia should be considered. In case of a high index of suspicion of a parastomal hernia, imaging is an important diagnostic tool besides physical examination.

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ORIGINAL ARTICLE

Hospital specific factors affect quality of blood pressure treatment in chronic kidney disease

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ABSTRACT

Background: Blood pressure (BP) is the most important modifiable risk factor for cardiovascular (CV) disease and progression of kidney dysfunction in patients with chronic kidney disease. Despite extensive antihypertensive treatment possibilities, adequate control is notoriously hard to achieve. Several determinants have been identified which affect BP control. In the current analysis we evaluated differences in achieved BP and achievement of the BP goal between hospitals and explored possible explanations.

Methods: At baseline, BP was measured in a supine position with an oscillometric device in 788 patients participating in the MASTERPLAN study. We also retrieved the last measured office BP from the patient records. Additional baseline characteristics were derived from the study database. Univariate and multivariate analyses were performed with general linear modelling using hospital as a random factor.

Results: In univariate analysis, hospital was a determinant of the level of systolic and diastolic BP at baseline. Adjustment for patient, kidney disease, treatment or hospital characteristics affected the relation. Yet, in a fully adjusted model, differences between centres persisted with a range of 15 mmHg for systolic BP and 11 mmHg for diastolic BP.

Conclusion: Despite extensive adjustments, a clinically relevant, statistically significant difference between hospitals was found in standardised BP measurements at baseline of a randomised controlled study. We hypothesise that differences in the approach towards BP control exist at the physician level and that these explain the differences between hospitals.

KEYWORDS

Chronic kidney disease, therapeutic inertia, centre differences, blood pressure, epidemiology

INTRODUCTION

Blood pressure (BP) is considered to be the most important modifiable cardiovascular (CV) risk factor. In large population studies a reduction of systolic BP of 20 mmHg is associated with a 33% reduction in stroke and ischaemic heart disease in patients aged 80 to 89 years and an even greater reduction of 62% in stroke and 51% in ischaemic heart disease in those aged 50 to 59 years.[1] The prevalence of hypertension is high in patients with chronic kidney disease (CKD) and increases with CKD stage from 79% in CKD stage I to 95% in CKD stages IV and V.[2] In patients with CKD, reduction of BP is not only important to prevent CV events but also to attenuate the decline of kidney function.[3,4]

Nowadays, physicians can use a multitude of effective BP-lowering agents and, in addition, focus on lifestyle

changes. Despite this armamentarium, the large majority of patients do not achieve treatment goals.[5-7] Several factors have been identified to be associated with poor BP control, including more advanced kidney dysfunction, poor adherence, absence of health insurance and physicians not adhering to guidelines or showing therapeutic inertia.[5,8-10] Recently, we reported in CKD patients that the hospital where a patient receives treatment was independently associated with a quality of care score based on 11 different risk factors.[11] In the current analyses, we evaluated the BP and the degree that BP goals were achieved, compared results between centres and explored possible explanations for the observed differences.

SUBJECTS AND METHODS

MASTERPLAN study

The MASTERPLAN study [Trial registration ISRCTN registry: 73187232 (http://isrctn.org)] is a randomised, controlled trial conducted in nine hospitals with a nephrology department in the Netherlands. Rationale and design have been published elsewhere.[12,13] Ethical approval was given by the ethics board of the University of Utrecht with additional endorsement of local applicability by the ethical boards of each of the participating hospitals.

In brief, adult patients with CKD (estimated GFR between 20 and 70 ml/min) were included in the study.

The effects of a multi-targeted treatment regimen executed by a specialised nurse under the supervision of, and in collaboration, with a nephrologist are compared with the care delivered by the patients own physicians, also mostly nephrologists. In both arms of the study, the same sets of guidelines apply. The primary endpoint is a composite of fatal and nonfatal myocardial infarction, stroke and cardiovascular mortality. Secondary endpoints are all-cause mortality, achievement of treatment goals for the various risk factors, decline of kidney function and quality of life. Follow-up will continue for five years.

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

Patient evaluation

Baseline measurements consisted of a questionnaire to obtain information on smoking behaviour, physical activity and medication use. Physical examination consisted of measurement of height, weight and BP (oscillometric BP measurements after 15 minutes of supine rest, mean of five measurements in the following 15 minutes). BP was concluded to be on target if oscillometric BP level was ≤125/80 mmHg in patients without proteinuria and ≤120/70 mmHg in patients with ≥1 g proteinuria / 24 hours (guidelines indicate goals of 130/85 and 125/75 mmHg respectively for office measurement; an additional 5 mmHg adjustment for both systolic and diastolic BP is applied for the period of supine rest and use of an oscillometric device).[14,15] Also the BP of the patient measured during the last outpatient visit prior to randomisation (screening visit) was retrieved. These were sphygmomanometric office measurements, usually taken in a sitting position by an experienced internist during the visit to the centre. The sphygmomanometric devices were of the aneroid mechanical type.

All devices (both oscillometric and sphygmomanometric) are validated annually in participating centres. Aneroid devices were validated by local technical services in the respective centres. Most centres retained a mercury sphygmomanometer in their technical department to allow for correct validation. Additional validation of the oscillometric devices was performed prior to the start of the study. Per centre different types of oscillometric devices are used: BP100 (Gambro, Lund, Sweden), Critikon (Critikon, Tampa, Florida), Dinamap Procare (GE Medical Systems Information Technologies Inc., Milwaukee, Wisconsin), Accuratorr plus (Datascope, Mahwah, New Jersey).

Blood was drawn and a 24-hour urine sample was collected. Blood and urine samples were analysed by the centre's laboratory. Medical history was obtained from the medical records. History of CV disease was defined as a history of myocardial infarction, stroke or vascular intervention. Diabetes mellitus at baseline (DM) was defined as the use of glucose-lowering drugs or a fasting glucose >7.0 mmol/l. Adherence to the Dutch Guidelines of Healthy Physical Exercise was determined with the validated SQUASH questionnaire.[16] The underlying diagnosis of kidney disease was determined by the treating physician and categorised using the ERA-EDTA (European Renal Association) registration criteria. To allow comparisons with other studies, we report the estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.[17]

Data analysis

Baseline characteristics were given for the study population by participating hospital and expressed as means (SD) or proportions. For non-parametric data medians [range] were supplied. Differences between centres in risk factors were studied using analysis of variance adjusted for age and gender if applicable.

With regard to missing data, two analyses were performed: one complete case analysis (all complete data) and one in which missing data were imputed. The presented data

are based on imputed data. Five separate imputations were performed and analyses were carried out on each imputation separately.[18] Results were then pooled via the statistical software (SPSS 17).

Since patients cluster within hospitals, we applied general linear modelling for continuous dependent variables and included hospital as a random effect.[19] As a measure for the explanation of the variability in the model η^2 is used, since for this type of analysis η^2 is considered more appropriate than R^2.

For multivariate analyses of the centre effect, different models have been constructed. Based upon known determinants of systolic and diastolic BP, both from literature and our own analyses, we came to the following models (which can be viewed online as appendix A):

Model 0: no adjustment;

Model 1 (patient characteristics): age, gender, race, history of CV disease, history of DM, body mass index (BMI), income, current smoking, physical activity, left ventricular hypertrophy (LVH) on ECG;

Model 2 (additional kidney disease characteristics): Model 1 + diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium;

Model 3 (additional treatment characteristics): Model 2 + sodium excretion in urine, number of visits in the year prior to randomisation, number of antihypertensives, renin angiotensin system (RAS) intervention, use of diuretics;

Model 4 (additional hospital characteristics): Model 3 + hospital size, academic status.

Adjusted means were calculated for systolic and diastolic BP measured at baseline and at the screening visit. Adjustment was performed for age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG, nephrological diagnosis, history of kidney transplantation, eGFR, proteinuria, sodium excretion in urine, number of visits in the year prior to randomisation, number of antihypertensives, RAS intervention, use of diuretics and hospital size. The analyses were performed with SPSS 17.0 (SPSS inc., Chicago, USA).

RESULTS

A total of 793 patients were included in the study between April 2004 and December 2005. Three patients did not meet inclusion criteria and two patients withdrew consent directly after randomisation, leaving 788 patients available for the analyses.

Baseline characteristics are given in *table 1*. The majority of patients are male (68%) and Caucasian (92%). Mean BP is 135 (±20)/78 (±11) mmHg. The proportion of patients considered to have achieved the treatment goals based on the oscillometric BP measurement is 28%, varying between centres from 12 to 42% *(table 1)*.

Differences in BP between hospitals

In the general linear modelling analysis with centre as a random factor, systolic BP was significantly lower in all hospitals compared with the reference centre (Centre B) *(table 2a)*.

Models 1 and 2 showed that some of the differences are explained by patient and kidney disease-related characteristics, respectively *(table 2a)*. Factors added in models 3 and 4 did not seem to contribute much. For diastolic BP, patient-related characteristics (Model 1) have the greatest contribution. Adjustment for pharmacotherapy (i.e. the use of RAS intervention (either an ACE inhibitor or angiotensin receptor blocker) or diuretics) did not explain the differences between hospitals (Model 3). A table with the results of the various models can be viewed online as appendix B.

In the final full multivariate model (Model 4) a clear centre effect remained present, i.e. hospitals A, C, D, G and H showed significantly lower systolic BP levels compared with the reference centre. The centre effect explained about half of the variability that can be explained by the regression model; η^2 for the full model is 0.21 and 0.10 for the model without adjustments. Also in a reverse fashion for the fully adjusted model without centre η^2 was 0.13, whereas the fully adjusted model with centre had an η^2 of 0.21. The range of the differences in adjusted systolic BP between hospitals was 15 mmHg.

For diastolic BP a centre effect was found with centre I having the highest diastolic BP and centre G the lowest (*table 1*, appendix B). After adjustment for additional determinants the differences remained. The difference between highest and lowest diastolic BP after adjustment is 11 mmHg. Hospitals A, D, E and G also had a significantly lower diastolic BP compared with hospitals F and I.

Differences in oscillometric and sphygmomanometric (office) BP measurements

Based on the previous findings we performed additional analyses to explore the following issues as potential explanations of these findings.

1. Are there not only centre differences in the oscillometric BP measurements (BP obtained with the BP measuring device at baseline of the study), but also in the sphygmomanometric BP measurements performed at the outpatient clinics during the last visit prior to entry into the study (median 32 days before inclusion (IQR 20-53 days). *Figure 1* shows that on average oscillometric BP is lower than office BP (p=0.05 for systolic BP and p=0.006 for diastolic BP). Yet, the centre effect remained present in both methods of BP assessment.

Table 1. *Baseline characteristics of the MASTERPLAN cohort*

Variable	Total (n=788)	A (n=94)	B (n=100)	C (n=100)	D (n=100)	E (n=104)	F (n=91)	G (n=66)	H (n=65)	I (n=68)
Age (years)	59.1 (13.0)	54.3 (13.2)	60.9 (11.6)	59.3 (11.8)	52.5 (12.6)	59.9 (13.2)	61.9 (10.5)	66.9 (12.6)	58.5 (14.3)	60.3 (12.2)
Gender (male %)	68	64	76	76	68	59	77	64	55	66
Caucasian (%)	92	93	95	94	99	73	95	88	95	100
KTR (%)	14	32	3	10	30	14	8	3	0	21
Prior CV disease (%)	29	29	38	30	16	29	36	30	23	34
Cause of kidney disease (%)										
Unknown	20	31	20	52	8	12	20	14	14	4
Glomerulonephritis	15	16	6	17	31	14	7	8	14	22
Interstitial	9	11	5	6	23	8	4	5	11	3
Cystic	10	18	7	5	13	4	8	6	20	12
Other cong	2	3	0	0	7	1	0	0	5	3
Renovascular	27	6	49	15	4	43	35	42	11	38
Diabetes	10	9	9	4	9	12	14	18	5	16
Other multisystem	5	4	3	1	3	4	8	3	19	2
Other	2	2	1	0	2	4	4	5	3	0
BMI (kg/m^2)	27.1 (4.7)	26.1 (4.6)	26.7 (4.2)	28.6 (4.5)	27.1 (5.6)	27.2 (5.3)	27.2 (4.0)	27.6 (5.1)	25.6 (4.3)	27.3 (4.0)
Oscillometric BP (mmHg)	135(20)/78(11)	127(16)/75(8)	145(22)/82(12)	136(18)/80(10)	128(16)/76(8)	140(23)/77(11)	140(19)/81(9)	131(25)/72(10)	128(19)/76(13)	141(17)/84(11)
Office BP (mmHg)	137(20)/79(10)	132(17)/82(9)	145(23)/81(8)	138(23)/80(11)	135(15)/79 (7)	134(20)/79(11)	139(23)/78(11)	135(23)/73(12)	134(19)/79(10)	138(16)/80(8)
No. of visits in year prior to inclusion	3 [0-31]	3 [1-31]	2 [0-5]	3 [1-8]	4 [2-31]	3 [0-8]	3 [0-8]	3 [0-8]	3 [0-10]	3 [1-8]
Creatinine (µmol/l)	182 (68)	201 (74)	186 (68)	182 (55)	168 (83)	184 (83)	160 (58)	180 (78)	191(74)	188 (60)
eGFR by MDRD (ml/min/1.73 m^2)	37 (14)	33 (13)	37 (15)	36 (11)	40 (13)	38 (16)	44 (16)	37 (13)	34 (11)	34 (10)
Proteinuria (mg/24 h)	300 [0-9300]	400 [100-9300]	163 [0-7000]	300 [20-7400]	600 [0-6640]	221 [0-9000]	100 [0-3700]	300 [0-6800]	400 [30-7000]	305 [0-6300]
Urinary sodium excretion (mmol/24 h)	150 [29-419]	139 [29-261]	158 [57-283]	162 [51-419]	160 [46-340]	129 [31-343]	148 [44-297]	130 [34-279]	148 [48-318]	163 [48-366]
Serum potassium (mmol/l)	4.4 (0.6)	4.5 (0.6)	4.5 (0.6)	4.2 (0.5)	4.7 (0.6)	4.7 (0.5)	4.3 (0.5)	4.3 (0.6)	4.5 (0.6)	4.4 (0.5)
LVH on ECG (%)	15	21	13	22	10	21	11	9	5	13
Monthly income (euro)	1900 [1000-8500]	2100 [1000-7000]	1880 [1200-3900]	1900 [1100-3400]	1970 [1200-4900]	1800 [1000-4700]	1800 [1100-4000]	2050 [1200-5100]	1900 [1100-8500]	1900 [1100-2800]
Physical activity (met/min x min/week)	5190 [80-41940]	6460 [240-21480]	4020 [600-17340]	6420 [600-17340]	5430 [800-19765]	4690 [120-16380]	4920 [300-18300]	4400 [80-28560]	4974 [120-16800]	6000 [240-41940]
Smoking (%)	21	19	24	18	14	28	24	15	26	19
Antihypertensives										
No. antihypertensives	2.4 (1.3)	2.3 (1.0)	2.6 (1.5)	2.4 (1.3)	2.1 (1.2)	2.5 (1.3)	2.4 (1.4)	2.4 (1.4)	2.2 (1.3)	2.5 (1.2)
RAS intervention (%)	79	89	83	64	78	84	85	80	79	71
Beta-blocker (%)	50	37	57	63	57	45	43	39	42	62
Calcium channel blocker (%)	35	21	47	31	25	39	46	36	32	38
Diuretics (%)	50	60	45	56	37	56	40	53	46	60
Loop or thiazide (%)	49	59	44	54	37	53	36	53	46	57
Alpha-blockers (%)	9	3	15	7	1	17	11	8	8	10
Other antihypertensives (%)	1	0	1	3	1	1	2	0	0	0

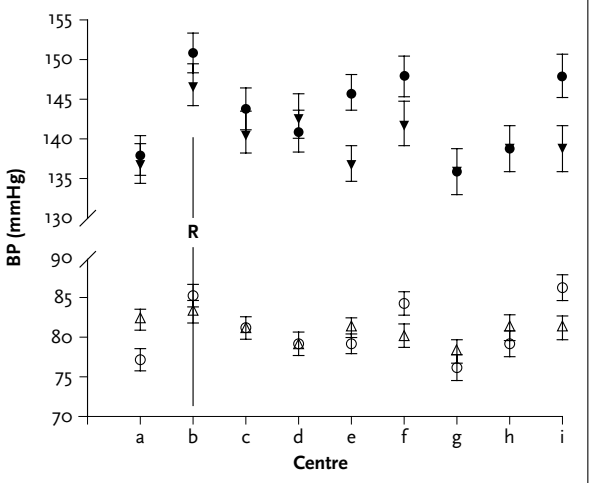
Values given are mean (SD) or % or median [range].
KTR = kidney transplant recipient; CV = cardiovascular; GN = glomerulonephritis; IN = interstitial nephritis; PKD = polycystic kidney disease; MDRD = modification of diet in renal disease; BP = blood pressure; BMI = body mass index; oscillometric BP = oscillometric assessment after 30 min of supine rest; office BP = sphygmomanometric BP during the last outpatient clinic prior to randomisation.

Table 2. *Univariate and multivariate general linear modelling for systolic BP with hospital as a random effect*

Centre	Model 0: η^2=0.10		Model 1: η^2=0.17		Model 2: η^2=0.20		Model 3: η^2=0.21		Model 4: η^2=0.21		
	B	p	B	p	B	p	B	p	B	p	95% CI
A	-18	<0.001	-15	<0.001	-15	<0.001	-13	<0.001	-13	<0.001	-19;-8
B	Ref		Ref		Ref		Ref		Ref		
C	-9	0.001	-9	<0.001	-8	0.004	-8	0.004	-8	0.004	-13;-2
D	-17	<0.001	-12	<0.001	-11	<0.001	-10	0.001	-10	0.001	-15;-4
E	-6	0.04	-6	0.02	-6	0.02	-4	0.11	-4	0.11	-9;1
F	-5	0.06	-6	0.04	-3	0.18	-3	0.20	-3	0.20	-9;2
G	-15	<0.001	-16	<0.001	-16	<0.001	-15	<0.001	-15	<0.001	-21;-9
H	-17	<0.001	-13	<0.001	-12	<0.001	-11	<0.001	-11	<0.001	-17;-5
I	-4	0.19	-3	0.30	-4	0.20	-3	0.30	-3	0.30	-9;3

Model 0: no adjustment; model 1: patient characteristics: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG; model 2: Model 1 + kidney disease specific: diagnosis, history of kidney transplantation, eGFR, proteinuria, serum potassium; model 3: model 2 + treatment related: sodium excretion in urine, no. of visits in the year prior to randomisation, no. of antihypertensives, use of renin angiotensin-modulating drugs, use of diuretics; model 4: model 3 + centre related: centre size, academic status. η^2 = is a measure of effect size for use in ANOVA, B = unstandardised regression coefficient (representing difference in BP in mmHg with centre B), p = p-value in statistical analysis.

Figure 1. *Adjusted BP values (according to model 4, table 2) in different centres*

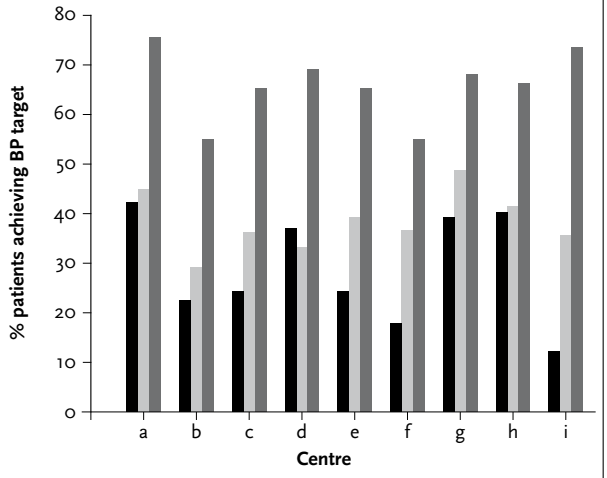


• = systolic oscillometric BP; o = diastolic oscillometric BP; ▼ = systolic office BP; Δ = diastolic office BP; ⊤ = 1 standard error of the mean. R = reference centre. Adjustment for: age, gender, race, history of CV disease, history of DM, BMI, income, current smoking, physical activity, LVH on ECG, nephrological diagnosis, history of kidney transplantation, eGFR, proteinuria, sodium excretion in urine, no. of visits in the year prior to randomisation, no. of antihypertensives, use of ACEs or ARBs, use of diuretics and centre size.

2. Do hospital differences disappear above a certain level of achieved BP goals? Such a finding might be interpreted as indicating that different targets are used in the hospitals. *Figure 2* shows percentages of patients achieving treatment goals per centre for three separate goals: a goal of 125/80 mmHg (120/70 mmHg if proteinuria >1 g/day) for oscillometric BP, a goal of 130/85 mmHg (125/75 mmHg if proteinuria >1 g/day) for sphygmomanometric office BP, and a goal of 140/90 mmHg for sphygmomanometric office BP (independent of proteinuria). *Figure 2* illustrates that differences between centres were present for all three treatment goals, although the smallest range was found when 140/90 mmHg as treatment goal is applied. In some centres a marked difference between achievement of the oscillometric BP goal and office BP goal could be appreciated (e.g. hospitals F and I) *(figure 2)*.

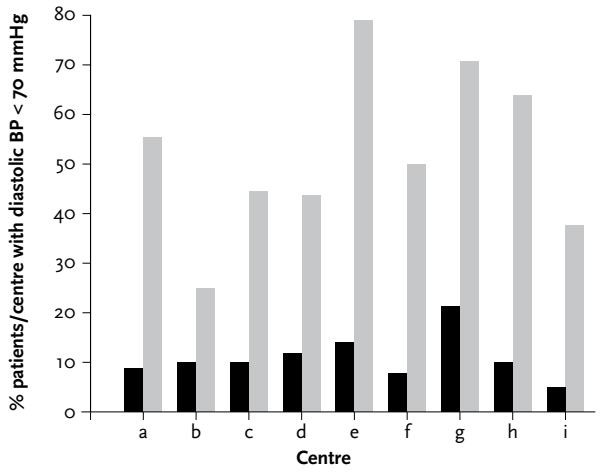
3. Could low diastolic BP be a factor obstructing achievement of treatment goals?
A diastolic BP <70 mmHg was present in 170 (21.6%) patients. This is shown per hospital for patients who do and do not meet the study treatment goal *(figure 3)*.

Figure 2. *Percentage of patients achieving BP goals in different centers*



Black bars represent the oscillometric BP goal, light grey bars represent the office guideline derived goals and dark grey bars represent a goal of 140/90 mmHg.

Figure 3. *Percentage of patients with diastolic BP <70 mmHg in different centres*



Black bars represent the patients not achieving the study treatment goal and the light grey bars represent patients who do meet the study goal.

In 62 of 587 patients not on target (10.6%) diastolic BP was below 70 mmHg with no significant differences between hospitals.

DISCUSSION

The present study shows that there are substantial and clinically relevant differences between centres with regard to achieved systolic and diastolic BP levels in CKD patients and percentages of patients achieving adequate BP control. These differences persist after adjustment for various patient, kidney disease, treatment and hospital characteristics.

Adequate BP control in hypertensive patients is notoriously difficult and may show important differences between populations. Even more so in the CKD population because of the added disturbed sodium and water handling. Differences between countries may be attributed to the use of different guidelines, differences in lifestyle factors, healthcare organisation and racial distribution.[20] In the present study, all patients were subject to the same set of guidelines, to the same healthcare organisation and mostly of Caucasian race. It seems fair to conclude that these factors cannot explain the differences observed between hospitals. In addition, potential differences in several lifestyle factors between patients in centres were taken into account in our analysis.

In the present analysis, we went at length to take possible confounders into account.[5] Patient characteristics including socioeconomic status (Model 1) and characteristics of kidney disease (Model 2) did contribute and explained partially the differences between hospitals. Treatment- and hospital-related factors (Models 3 and 4) did not markedly change the observed associations. The fact that BP-lowering therapy did not affect differences between centres may be explained by the high prevalence of the use of both diuretics and agents that interfere with RAS in all the hospitals. So, Model 4 showed that despite adjusting for multiple factors, differences between hospitals persist. These results necessitate the consideration of yet additional factors, which may be of relevance.

Firstly, we addressed the question whether the technique/device is the source of the difference. For that purpose, we also studied the last BP measured by the physician during the visit to the outpatient clinic prior to inclusion (a manual sphygmomanometric measurement using an aneroid device). *Figure 1* showed that these office BPs substantially differed between hospitals, indicating that the observed difference between hospitals was not explained by the different oscillometric devices. Moreover, BP differences existed between centres that use the same oscillometric device (e.g. centres A and I both used the Datascope device, centres D, E, G an H all used the Critikon device).

It must be noted that in some centres a marked difference between oscillometric BP and office BP was present. This might indicate that the technique and situation of measurement affected results to a certain extent as stated recently by Becker and Wheeler, although all office measurements were performed in the office during the visit by the internist using an aneroid sphygmomanometric device *(figure 2)*.[21] A second factor is that a yet unmeasured patient characteristic may have (partially) contributed to the centre effect. These factors may include ethnicity, living environment and adherence to the prescribed treatment. Our cohort included patients from North-Africa, the Middle-East, Turkey and Northern Europe and all these different ethnicities were classified as Caucasian. The prevalence of these ethnicities is variable in the various regions of the Netherlands and may have been different between hospitals, which might have affected the results.[22,23] Non-adherence to therapy is a well-known cause for not achieving BP goals and may be different between hospitals and possibly also affected by ethnicity.[24,25] Also environmental issues (i.e. crime, street noise, crowded housing) could affect BP and be distributed unevenly between the regions in which the hospitals are located.[23] However, these factors have not been specifically addressed in this study.

A third and most relevant factor in explaining the centre differences may have been the attitude of the physician towards BP management. We have analysed the data at the level of the hospital, not the physician. As such detailed data have not been collected in the MASTERPLAN study, the

present dataset does not allow such an analysis. The hospitals were, however, comparable with regard to the number of visits and the number or type of prescribed antihypertensive agents. Although all physicians had access to and were familiar with the same set of guidelines, we unfortunately had no data on the target levels of BP that physicians in hospitals actually pursue.[26] Part of the observed differences could therefore be explained by different treatment goals: for example, in one hospital the physicians might target BPs below 130 mmHg systolic, whereas in another hospital a systolic BP of 140 mmHg was considered adequate. *Figure 2* showed that centre differences appeared less obvious when applying a goal of 140/90 for the office BP measurement, possibly illustrating this phenomenon. Since the difference between hospitals was still statistically significant, this factor does not fully explain the hospital effect.

The perceived importance of BP control could differ between physicians and hospitals and might possibly explain centre differences. Physician inertia (i.e. the tendency not to adjust the intensity of treatment, despite the fact that a risk factor does not meet the treatment goal) has been identified as an important factor affecting BP control and is also part of the physician attitude towards BP management.[8,9] However, as no information has been collected on these aspects, it was not addressed in this study.

A fourth aspect that could have affected treatment efficacy was the attainment of a low diastolic BP. Several studies have cautioned against lowering diastolic BP below 70 mmHg, especially in patients with vascular disease. This trend may hamper treatment of patients with high pulse pressure, since adequate lowering of systolic BP in these patients will often cause diastolic BP below 70 mmHg. Our data did not allow for a definite conclusion on this issue.

LIMITATIONS

Our study has some limitations. The present analysis was performed on baseline data of CKD patients who consented to participate in a randomised controlled trial. Therefore, the results might not be generalisable to the general CKD population. Further, all automated devices were validated within the centres, but were not all from the same manufacturer. We cannot exclude the possibility that this is of relevance.

Finally, at the start of the study, we did not expect to find this centre effect. Therefore, we may not have collected sufficient data to evaluate this finding in much more depth; for instance, daily defined dosages of antihypertensives could have illustrated some differences in treatment. Because of the numerous different antihypertensives applied in the cohort at baseline, daily defined dosages could not be calculated. However, it seems reasonable to assume that this centre effect is to be explained on the level of the physician.

In conclusion, the present data indicate that there are substantial and most likely clinically relevant differences between centres in the quality of BP control in CKD patients. Our analysis suggests that this may be explained by differences at the level of the physician. Further studies are necessary to address this possibility in more detail. It is attractive to hypothesise that this reveals additional opportunities to improve the quality of care.

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CONFLICTS OF INTEREST/DISCLOSURE

None.

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CASE REPORT

Episodes of shortness of breath induced by prednisone

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ABSTRACT

Although anecdotal reports pointing to the occurrence of episodes of shortness of breath due to prednisone use have been published, systematic evidence is lacking. In this manuscript we report on an n=1 trial in a patient using prednisone for polymyalgia rheumatica. With this approach we can confirm that prednisone may cause episodes of dyspnoea and we provide potential explanations for this side effect.

KEYWORDS

Shortness of breath, hyperventilation, prednisone

INTRODUCTION

Prednisone has been used effectively in many diseases and is prescribed frequently by many doctors. Prednisone is known to cause many side effects. Its use may lead to the development of diabetes mellitus, osteoporosis and myopathy in skeletal muscles and in muscles involved in respiration.[1] Although many patient stories on the internet describe that use of prednisone may lead to transient episodes of shortness of breath accompanied by hyperventilation, this has not been described in medical literature. Through a so-called N-of-1 study we describe an association between prednisone and shortness of breath.

CASE REPORT

A 71-year-old woman complained of pain in the upper and lower extremities. She had difficulty in combing her hair and the pain was associated with extreme tiredness and morning stiffness. A diagnosis of polymyalgia rheumatica (PMR) was made. Her complaints decreased shortly after high dosages of prednisone.

A few weeks after starting prednisone the patient complained of shortness of breath at rest and on mild exertion. The patient had the feeling that she could not inhale enough oxygen. Her past history was uneventful and she had smoked cigarettes until 32 years ago (about 20 pack-years).

During a routine outpatient visit (with use of 20 mg prednisone a day) the patient had a breathing frequency at rest of 26 per minute. Blood gas analysis showed a respiratory alkalosis (pH 7.63; pCO_2 17 mmHg; HCO_3- 17.4 mmol/l and pO_2 132 mmHg (*table 1*; normal values). A possible cardiac cause was excluded after a thorough cardiological examination (ECG, echocardiogram, cardiac MRI and coronary angiography were normal). A pulmonary cause was also considered unlikely (X-thorax, lung function test, exercise testing and right catheterisation were all normal). All the tests were performed while she was taking prednisone.

Her breathlessness decreased when the dose of prednisone was lowered. When she had an exacerbation of the PMR it was always necessity to increase the dose of prednisone, as the other therapeutic options, such as non-steroidal anti-inflammatory drugs and methotrexate, were unable

Table 1. *Normal values blood gas*

pH	7.35 – 7.45
pCO_2	35 – 45 mmHg
$pHCO_{3^-}$	22 – 26 mmol/l
BE	-2.0 – 3.0 mmol/l
pO_2	75 – 100 mmHg
O_2 saturation	0.92 – 0.98

BE = base excess

to control the PMR symptoms. As an increase in the dose of prednisone clearly led to an increase in her shortness of breath, we hypothesised that prednisone was the cause of the dyspnoea.

N-OF-1 STUDY

To demonstrate the association between prednisone and shortness of breath, one of the authors undertook a total of five home visits to the patient. During this period the patient's condition was stable. Because of the PMR symptoms, she was taking 2 mg prednisone every morning. The patient was still experiencing PMR symptoms with this dosage, but was unwilling to take the higher dose because of the shortness of breath associated with higher dosages of prednisone. However, she did take 4 mg of prednisone when the pain was severe. The patient noticed a clear increase in her shortness of breath when she took the higher dose. The time between taking the (extra) prednisone and the shortness of breath was about six hours and disappeared after 12 to 14 hours.

We therefore decided to test whether there was a linear association between the prednisone dosage and her respiratory symptoms. This was achieved by measuring several parameters while she was taking different amounts of prednisone: three measurements with the normal dose of 2 mg, and one measurement with 4 mg and 8 mg, respectively. The parameters that were measured included the Medical Research Council (MRC) dyspnoea scale (grade 1 (not troubled by breathlessness except on strenuous exercise) to grade 5 (too breathless to leave the house, or breathless when dressing or undressing)),[2] and the Karnofsky score (score 100: able to work and no complaints to score 10: moribund).[3] Other measurements recorded were breathing frequency at rest and after light exercise (after a walk of about 400 metres at normal speed). Blood gases were also analysed at two time points. The time of intake of prednisone was usually around 06.30 am. All measurements were taken between 4 pm and 8 pm. The results of the measurements are shown in *table 2*. At measurement 3, after ingesting 8 mg of prednisone, shortness of breath was so severe that the patient was unable to exercise.

Due to the intensity of pain experienced by the patient during the first arterial puncture it was decided to undertake a venous puncture during the second blood test. Analysis of the results showed a clear difference in both the breathing frequency at rest and breathing frequency after light exercise. There were also clear differences on the dyspnoea scale. The small difference between the outcomes on the Karnofsky score were attributed to the patient's PMR symptoms, meaning she was unable to perform several activities, independent of prednisone.

Blood tests showed that there was a respiratory alkalosis after ingestion of 8 mg prednisone and a normal blood gas after ingestion of 2 mg. The use of arterial and venous blood should not produce any differences given that the pH and bicarbonate percentage are comparable.[4,5]

DISCUSSION

PMR symptoms may lead to a situation where patients require (maintenance) doses of prednisone for many years.[6] This is already known to be associated with numerous symptoms. However, the relationship between episodes of shortness of breath and prednisone has not been previously described in medical literature. But when we did a simplified search through the use of Google (and search with the terms prednisone and shortness of breath or breathing difficulties) this relationship is mentioned

Table 2. *Results of measurements*

	BF/min in rest	BF/min after light exercise	Grade shortness of breath (MRC dyspnoea scale)	Functional limitation (Karnofsky) (%)	Blood gases
Measurement 1 (intake 4 mg prednisone)	16	24	4	70	
Measurement 2 (intake 2 mg prednisone)	14	18	2	80	
Measurement 3 (intake 8 mg prednisone)	18	-	5	70	Arterial: pH 7.48; pCO_2 30; HCO_3 21.8; BE -0.3; pO_2 70; O_2 saturation 0.96
Measurement 4 (intake 2 mg prednisone)	14	18	2	80	Venous: pH 7.37; HCO_3 27.0
Measurement 5 (intake 2 mg prednisone)	14	20	2	80	

BE = base excess; BF = breathing frequency.

several times. We tried to objectify the relationship between episodes of shortness of breath and prednisone with the abovementioned N-of-1 study.

The most plausible explanation for the increase in respiratory rate is that prednisone may pass through the blood-brain barrier and stimulate the breathing centre. Another hypothesis was that the shortness of breath was due to hyperventilation induced by psychological effects. However, her breathlessness only developed several hours after the intake of prednisone and also disappeared after a few hours. So, in our opinion, this hypothesis is not plausible. A myopathy of the breathing muscles as a potential cause of the symptoms is also implausible, mainly because the complaints were episodic.

The above N-of-1 study shows that prednisone side effects should be considered when a patient presents with shortness of breath. Our case has demonstrated that it took numerous consultations before the cause of the symptom became clear. Furthermore, it took many, very expensive, additional examinations, which in retrospect were not necessary.

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CASE REPORT

Cardiac involvement in hypereosinophilic syndrome

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ABSTRACT

Hypereosinophilic syndrome is a heterogeneous group of disorders characterised by hypereosinophilia and organ involvement of varying intensity. We describe involvement of the heart in patients with hypereosinophilic syndrome, and the diagnostic and therapeutic clinical management of these patients.

KEYWORDS

Hypereosinophilic syndrome, chronic eosinophilic leukaemia, cardiac magnetic resonance imaging, troponin

What was known on this topic?
In the last decade, molecular biology studies elucidated the aetiology of some variants of hypereosinophilic syndrome (HES), therefore reducing the group of patients with idiopathic HES and making targeted treatment possible. Cardiac involvement is common and may lead to restrictive cardiomyopathy.

What does this add?
Cardiac MRI has recently emerged as a non-invasive imaging modality and can be used for tissue characterisation and may obviate biopsy. Increased concentrations of troponin in HES is suggestive of acute inflammation of the endomyocardium.

INTRODUCTION

In 1968 the term hypereosinophilic syndrome (HES) was introduced to describe a heterogeneous group of diseases characterised by unexplained hypereosinophilia and organ involvement in varying degrees.[1] In 1975 Chusid was the first to establish three diagnostic criteria for HES: a persistent eosinophilia of 1500 eosinophils/mm^3 for longer than six months (1) with lack of evidence for allergic, parasitic or other known causes of eosinophilia (2) and symptoms and signs of organ involvement (3).[2] Nowadays this definition is still valid.[3] Many organ systems are affected in HES, but cardiovascular complications are most prevalent and are responsible for the observed high mortality.[4]
On the basis of a case report we discuss the nomenclature, the cardiac involvement in HES, the (new) diagnostic modalities and its treatment.

CASE REPORT

A 52-year-old male without previous medical history presented to the emergency department because of acute confusion. He was found in the shower, did not know how to shave and felt slightly dizzy. In the previous weeks he had been paranoid, tired and walked slowly with a forward-flexed posture. During the last year he had experienced a blurred vision hampering driving and using his mobile phone. For two months he had been taking acetaminophen because of bitemporal headache. He did not have any fever, chest pain, palpitations, dyspnoea or oedema. On physical examination he was not acutely ill, was haemodynamically stable, had no fever and lacked disease awareness. He undressed clumsily and slowly and complete examination only revealed a rigid gait with decreased arm swing and a slight apraxia of his left hand. Laboratory examination showed a haemoglobin of 7.2 mmol/l, leukocytes 21*10^9/l with 63% esosinophils in the differentiation (on several occasions), and a thrombocyte count of 198*10^9/l. C-reactive protein was 89 mg/l, creatinine 113 µmol/l (MDRD 59 ml/min/1.73 m^2), troponin T 0.91 µg/l, creatine kinase (CK) 100 U/l, CK-MB mass 8.2 µg/l, lactate dehydrogenase 420 U/l, aspartate

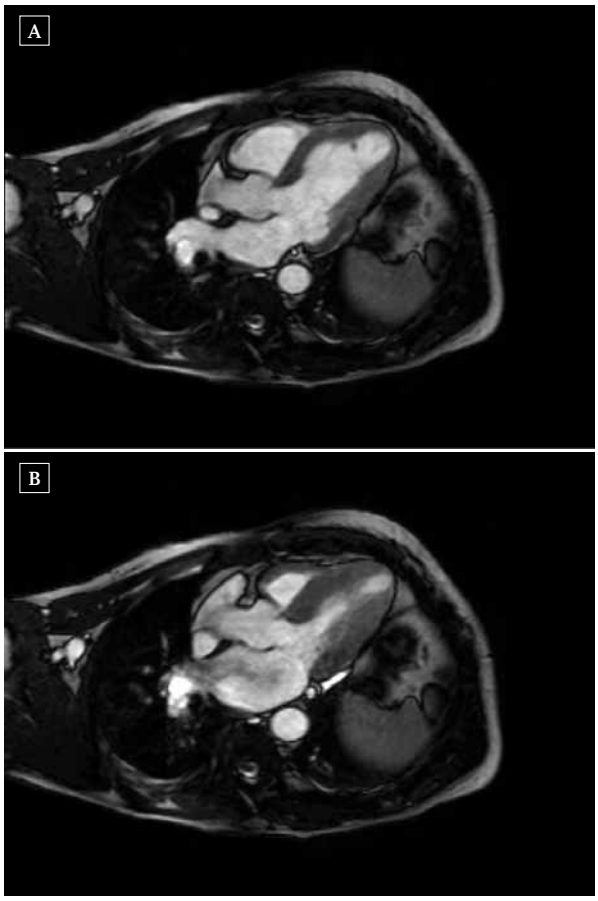
aminotransferase 37 U/l, and alanine transaminase 16 U/l. Vitamin B12 and tryptase were not elevated.

No parasitic infection, allergic or pulmonary disease were found as aetiology for the eosinophilia. Bone marrow aspirate showed 34% eosinophils, a normal percentage of blasts and many megakaryocytes in different developmental stages. No dysplastic features were present. Bone marrow biopsy was in part rich in cells with increased myelopoiesis and eosinophilia and in part hypoplastic accompanied by reticulin fibrosis. No infiltration of mast cells was visualised. To find chromosomal abnormalities associated with chronic eosinophilic leukaemia (CEL), fluorescent in situ hybridisation (FISH) examination of bone marrow cells was performed. However, a fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRα (PDGFRA) gene generated by an interstitial deletion on chromosome 4q12 was absent. On brain MRI extensive white matter lesions were present in the occipital lobes and periventricularly near the vertex of both areas vascularised by both medial cerebral arteries and in the right cerebellar hemisphere. Examination revealed decreased visual acuity but a normal ocular system. A CT scan was negative for lymphomas; only a mild splenomegaly was seen.

His ECG showed sinus rhythm, normal PQ time, normal heart axis and a QRS width of 0.09 seconds with a QS complex in V1 and V2, slight ST elevation in V2 and minimal ST depression in V4 to V6 with T-wave inversions in III, aVF, and V3 to V6. Cardiac ultrasonography showed slight left atrial dilatation and minimal mitral regurgitation. Systolic function was preserved. Diastolic dysfunction could not be excluded nor identified. Normal coronary arteries were visualised on a coronary artery angiography.

Because of the suspicion of a hypereosinophilic syndrome (HES) with neurological and cardiac involvement 60 mg prednisone was started three days after admission, even before all the tests had been performed. The concentration of troponin T rapidly decreased and was no longer detectable after ten days. Because of the persistent eosinophilia three weeks after the introduction of prednisone the tyrosine kinase inhibitor imatinib 400 mg per day was initiated. Simultaneously the prednisone was tapered to 2.5 mg during two and a half months. Within several weeks the hypereosinophilia had decreased significantly. A few days after imatinib was started (three and a half weeks after initiation of the prednisone) a cardiac MRI (CMR) was performed. On T2 weighed images apical subendocardial intensity was seen. On delayed enhancement images subendocardial enhancement of the apex was present. Hypokinesia of the apex of the left ventricle was visible. There were no signs of intracardial thrombus formation *(figure 1)*. Four months later the CMR was repeated and depicted the same subendocardial delayed enhancement following gadolinium. The apical T2 signal had disappeared. Troponin T remained within normal limits during follow-up. During follow-up of 12 months, no symptoms or signs of heart failure developed and his cognitive function and vision improved.

Figure 1. *Panel A shows the left ventricle during diastole. During ventricular contraction apical hypokinesia is seen (panel B)*



DISCUSSION

Nomenclature

Developed in 1975, Chusid's criteria are still suitable for diagnosing HES nowadays. Hasn't anything changed in 30 years? On the contrary. The heterogeneous group of disorders constituting HES is decreasing as separate disease entities are recognised. A lymphocytic variant is distinguished by the presence of clonal populations of abnormal T cells producing interleukin-5 with subsequent production of eosinophils, making it a peripheral T-cell lymphoma.[5] Increased blast cells (but less than in acute leukaemia), evidence of clonality or the presence of a fusion gene, particularly the fusion of FIP1L1 and PDGRFA caused by a deletion on chromosome 4q12, are diagnostic of CEL.[3,6] This fusion gene encodes for a protein with substantial tyrosine kinase activity which has important implications for therapy. Rearrangements of other genes (PDGRFB and

FGFR1) may also be responsible for myeloid or lymphoid neoplasms with eosinophilia.[3] If a patient fulfils Chusid's criteria and no cause is found for the eosinophilia after thorough investigation, the WHO classifies this patient as having *idiopathic* HES even if there are features suggestive, but not diagnostic, of a myeloproliferative/leukaemic disorder (dysplastic eosinophils on peripheral smear, serum vitamin B12 >000 pg/ml, serum tryptase ≥2 ng/ml, anaemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity >80%, spindle shaped mast cells, myelofibrosis).[3] It is said that the term 'hypereosinophilic syndrome' should be discouraged as a diagnostic term since this term indicates either an imprecise use of language or that the patient has not been adequately investigated.[7] However, when using the (older) literature and during the diagnostic process it is inevitable to use the term hypereosinophilic syndrome. According to WHO classification our patient should be classified as having idiopathic HES.

Cardiac involvement

Pathogenesis of cardiac disease

Cardiac involvement in HES is rare in the lymphocytic variant of HES but often occurs in the myeloproliferative forms.[8,9] The overall prevalence of cardiovascular involvement is over 50%.[10] Cardiac disease follows three stages.

The first is an acute necrotic stage due to infiltration of eosinophils in the myocardium. The contents of the eosinophilic granules (eosinophilic major basic protein, eosinophilic cationic protein and eosinophil protein-X) are present within the endocardium and myocardium and are held responsible for the initiating the damage.[11] Little information is available about the duration of this stage, but a mean of 5.5 weeks with a range of one day to three months has been reported based on the duration of cardiac symptoms.[12] However, this stage is thought to be asymptomatic in many cases, which hampers the determination of the actual course of this stage.[9]

The intermediate phase is characterised by mural thrombi and thrombus formation along the damaged endocardium (thrombotic stage).[11,12] The left ventricle is more often affected and thrombi tend to be located in the apices where stasis is more of a factor.[2,9] Patients with thrombotic lesions have an average duration of symptoms of ten months.[12] This is followed by organisation of the thrombus into a thick layer of granulation tissue which replaces the normal endocardium. The third stage is the later fibrotic stage in which the granulation tissue is changed into hyaline fibrosis, sometimes still with a small inflammatory zone in deeper layers.[11,12] In comparison with the acute stage, there are no or minimal deposits of eosinophil granule proteins, suggesting that the fibrotic stage represents the final stage of a pathogenetic sequence initiated by myocardial eosinophilic infiltration.[11]

Löffler called the combination of this peculiar cardiac disease and eosinophilia 'fibroplastic parietal endocarditis with blood eosinophilia'.[13] Nowadays Löffler's endo(myo)carditis is used to describe the involvement of the heart in HES, especially in the thrombotic and fibrotic stage.[14] This end stage is similar to that in other hypereosinophilic diseases affecting the heart (such as tropical endomyocardial fibrosis in tropical parasitic infections), proving the eosinophilia itself rather than the underlying condition is responsible for the damage.[12]

Symptoms and signs

By definition HES affects multiple organ systems. Cardiovascular manifestations are the most prevalent in HES with a prevalence of 50 to 60%.[4,10] As mural fibrosis develops the left ventricular compliance decreases resulting in a restrictive cardiomyopathy. Fibrosis affecting the papillary muscle and chordae tendinae may produce papillary dysfunction and mitral regurgitation.[15] As a consequence, in such patients symptoms and signs of heart failure can be present. The structural changes of the myocardium can provoke arrhythmias. Embolic events originating from the intracardiac thrombus are seen in up to 25%.[2,9,15]

Diagnostic modalities

Electrocardiographic alterations are common in HES. T-wave inversions are most frequently observed followed by premature ventricular beats and positive criteria for left ventricular hypertrophy. The T-wave inversion is thought to represent subendocardial injury due to endocardial fibrosis and inflammation.[15] Sporadically cardiac abnormalities in HES mimic acute myocardial infarction on the ECG.[14]

Endomyocardial thickening is seen in 68% of patients on echocardiography and is progressive. Apical obliteration due to thrombus formation and posterior mitral leaflet involvement are classical findings as well.[15] Evaluation by Doppler echocardiography can show a restrictive left ventricular filling pattern.[9] Pericardial effusion can be present.[2,15]

Coronary angiogram has no role in the diagnosis and shows no specific signs, but is occasionally used to exclude coronary artery disease.[14] Rarely, coronary artery spasms have been described.[16]

CMR is a useful technique with myocardial disease. Hyperintense myocardial area on T2-weighted images is suggestive of increased free-water content due to myocardial oedema and/or necrosis.[17] In HES this is particularly seen in ventricular apices. With the advent of the contrast-enhanced inversion-recovery MRI with late imaging superior contrast can be achieved between normal and abnormal myocardium.[18] Hyperenhancement of the non-ischaemic type in delayed enhancement cardiovascular magnetic assessment is both characteristic of fibrosis and an inflammatory exudate, and cannot be distinguished from each other without follow-up imaging. CMR has a high

sensitivity and specificity for detecting (apical) thrombi.[9] Overlying thrombus is identifiable as a low signal mass on the delayed enhancement images, which does not deform on tagged images. A characteristic three-layered image can be seen: a hypointense inner rim of thrombus adjacent to an hyperenhancement of the endocardium compared with the rest of the myocardium. Cardiac function is another important pillar of the assessment of myocardial disease. Regional areas of hypokinesia or akinesia and findings of restrictive cardiomyopathy (diastolic dysfunction with atrial enlargement and valvular regurgitation) can be visualised. The diagnostic yield of endomyocardial biopsy, the golden standard for establishing cardiac involvement, can be increased using CMR-guided biopsy.[17] Moreover, the high resolution of CMR makes tissue characterisation possible and the increasing experience makes CMR promising for diagnosis and follow-up.[19] Our patient had an increased subendocardial T2 signal in the left ventricular apex. Delayed enhancement following gadolinium also showed diffuse subendocardial enhancement. During follow-up apical T2 signals disappeared and delayed enhancement images were irreversible and subsequently proved to be fibrosis. If the imaging had been performed earlier, the abnormalities would probably have been more extensive and would have represented a combination of fibrosis and an inflammatory exudate.

Little is known about the use of troponin in HES. It seems to be more sensitive than CK-MB for inflammation in HES.[20] This is in line with a previous study concerning the sensitivity of CK-MB and troponin I in humans with myocarditis.[21] In three patients with biopsy-proven eosinophilic endomyocardial infiltration and normal echocardiography troponin T was initially elevated. It normalised after treatment with steroids, suggesting troponin T can be a sensitive marker for early cardiac damage and can gauge treatment.[20] In another study troponin T predicted acute myocardial decompensation before or soon after starting imatinib.[22] Prompt initiation of corticosteroids in these circumstances resulted in a rapid amelioration. It is advised to start adjunctive corticosteroids in patients with evidence of eosinophilic myocarditis who will start with imatinib.[22,23]
The initial rise in troponin T in our case was a marker of the necrotic stage of HES. It is likely the high dose of prednisone reduced the inflammation resulting in normalisation of the troponin T, even before the first CMR was performed.

Treatment

Corticosteroids have always been the cornerstone of the treatment of the different types of HES. A dramatic change has occurred since the discovery of the fusion protein with tyrosine kinase activity encoded by the FIP1L1-PDGRFA-fusion gene.[6] This fusion protein is very sensitive for the tyrosine kinase inhibitor imatinib. As demonstrated by our case some patients without the FIP1L1-PDGRFA genotype seem to benefit from imatinib, however usually with a slower response, indicating that an as yet unidentified mechanism of receptor tyrosine kinase is responsible for HES in these cases.[3,24] Other treatment options are hydroxyurea and interferon-α. The interleukin-5 antagonist mepolizumab has shown to be corticosteroid-sparing for patients negative for FIP1L1–PDGFRA, however its Marketing Authorisation Application in the European Union for the treatment of HES was withdrawn in 2009.[25] Novel therapies including alemtuzumab, a human monoclonal antibody directed against CD52 on eosinophils, have been reviewed recently.[26] The role of allogeneic stem cell transplantation is not well established, although some patients successfully underwent this treatment.[23] Response to treatment is normally fast. However, in cardiac disease the damage can only be reverted in stages with active inflammation and without anatomic alterations due to fibrosis.[23] Furthermore, treatment should be directed to heart failure and the presence of intracardial thrombus.
Absolute eosinophil count does not correlate in a consistent fashion with eosinophil-mediated tissue damage.[23] Unfortunately no validated markers of disease progression are available and therapy is monitored on the basis of a combination of clinical manifestations and absolute eosinophil count. Concerning cardiac disease endomyocardial biopsy is the gold standard, however sequential CMR may obviate the need for cardiac biopsy. In addition, troponin T seems promising in guiding treatment during the acute phase. However, more studies are needed to evaluate the diagnostic value of troponin T and more knowledge about troponin T in later stages of cardiac involvement is necessary.

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PHOTO QUIZ

A round air configuration in the lower abdomen

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CASE

An 81-year-old female was admitted with intermittent pain in the lower abdomen for one year, accompanied by episodes of rectal blood loss. Her lab results showed anaemia; infection parameters were within the normal limits. An abdominal X-ray *(figure 1)* shows a smooth-walled round air configuration with air-fluid level(→); barium enema *(figure 2)* revealed an air-filled structure (*) with barium entering this cavity.

Figure 1.

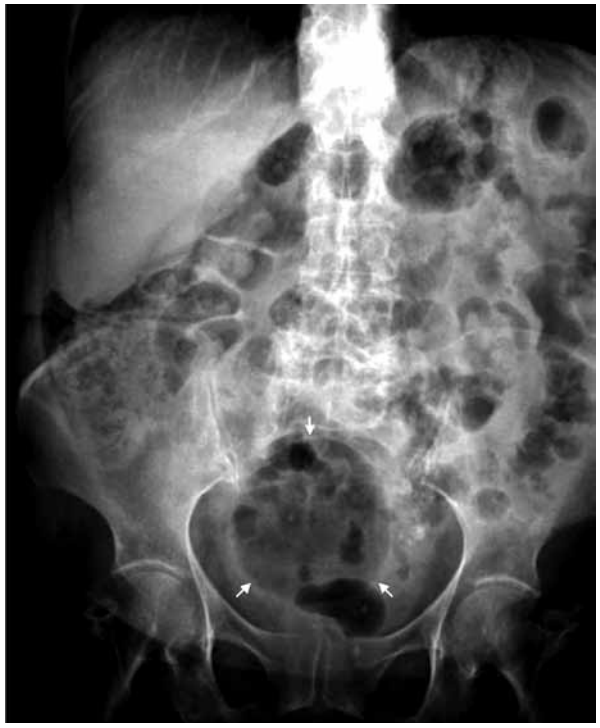
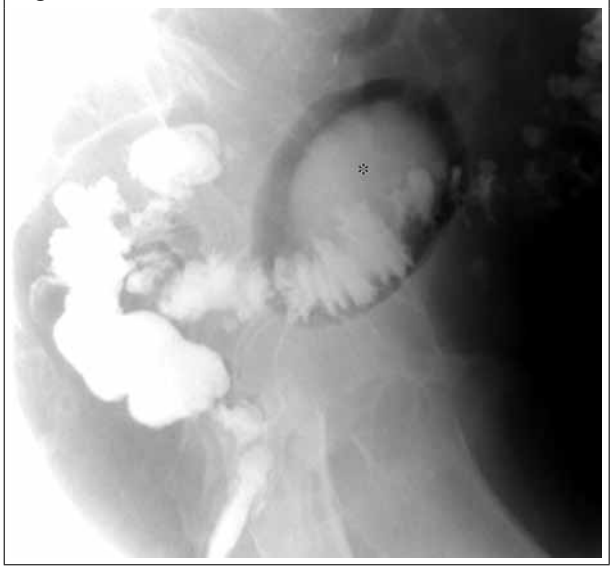


Figure 2.



WHAT IS YOUR DIAGNOSIS?

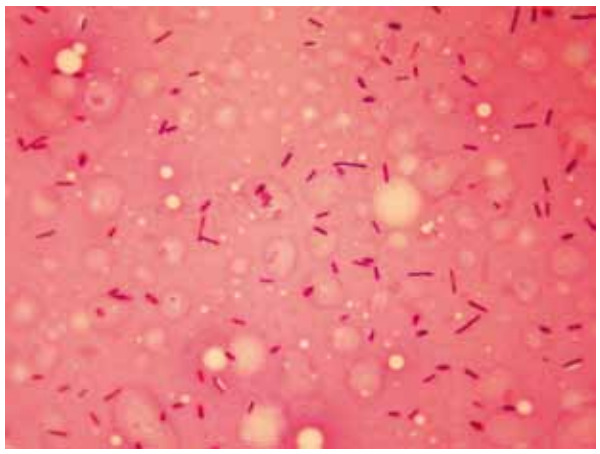
See page 247 for the answer to this photo quiz.

DIAGNOSIS

The presence of septic shock manifestations and rapidly progressive skin changes raised the suspicion of necrotising soft-tissue infection. Antibiotic therapy was immediately initiated with flucloxacillin, clindamycin and ciprofloxacin. Our diagnosis was confirmed during an acute surgical exploration, indicating extensive soft tissue necrosis spreading from the left arm to the back and the contralateral side. Complete debridement was judged impossible. Because of progressive septic shock and lack of treatment options, therapy was discontinued. The patient died several hours after presentation. Microbiological examination of blood and tissue cultures identified *Clostridium septicum* as the sole aetiological microorganism *(figure 2)*.

Life-threatening skin and soft-tissue infections (SSTIs) are infrequent and difficult to diagnose. Among gas-forming SSTIs, the pathogens most frequently responsible are *Clostridium* species.[1] Gas gangrene due to *Clostridium perfringens* or *C. septicum* following subcutaneous or intramuscular injection has infrequently been reported.[2] Our patient's history was unremarkable, apart from the depressive disorder. Particularly, there was no evidence of colorectal cancer or a compromised immune system. Although the initial abdominal pain and nausea in our patient might suggest an intestinal focus, it is more likely that they result from release of clostridial toxins, which has been related to gastrointestinal symptoms.[3] In our patient, fatal gas gangrene of the left shoulder developed three days after intramuscular injection of the H1N1 influenza vaccine in the left forearm, suggesting a causative association. This is further supported by an essentially similar case reported previously.[4] Presumably, in these cases clostridial spores infect muscle tissue where the response to vaccination favours relative hypoxia in which anaerobic *Clostridium* species can thrive.[2] Our report emphasises the fulminant evolution of gas gangrene and adds influenza vaccination to the list of conditions associated with the risk of gas gangrene development. At the same time, this is the first report on fatal *C. septicum* gas gangrene in an individual who received the H1N1 influenza vaccine.

Figure 2. *Gram-staining of a specimen taken from the skin during the surgical exploration showing the presence of Clostridium septicum at the site of gangrene*



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ANSWER TO PHOTO QUIZ (PAGE 245)

A ROUND AIR CONFIGURATION IN THE LOWER ABDOMEN

DIAGNOSIS

Sigmoidoscopy showed diverticulosis. CT showed a round, thick-walled structure adjacent to uterus, left ovary and sigmoid, measuring 8 cm, containing air and fluid *(figure 3)*. There were no signs of infection. Patient was operated upon and recovered uneventfully. Pathology revealed a collapsed cystic structure containing little blood, connected with the sigmoid lumen. It was concluded to be a giant colonic diverticulum (GCD).

DISCUSSION

GCD is rare: we counted 122 PubMed-cited cases in the last 30 years. The definition is an air and/or fluid containing cystic structure adjacent to the colonic wall measuring 4 cm or more; 80 to 90% are found appending the sigmoid. In the literature the size varies from 6 to 29 cm, the majority being <10 cm.[1,2]

Age at presentation is generally over 60 years. Presenting signs and symptoms are abdominal pain (68%) a (non) tender mass (68%), altered bowel habits (29%), fever (21%), rectal blood loss (8%), and signs of an acute abdomen (7%). Major complications are perforation and abscess formation.[1]

Although clinically indistinguishable, GCD can be divided into three subtypes: the first subtype (66%) has a thick fibrous wall without inner lining. These are considered the result of perforated diverticula with consecutive abscess drainage into the bowel. The second subtype (22%) are regarded as pseudo-diverticula. These are (partly) lined with mucosa, and remnants of muscularis mucosa are sometimes found within the wall. Enlargement is usually gradual, occurring through a ball-valve mechanism. Finally, 12% are true diverticula, containing all layers of bowel wall.[3,4]

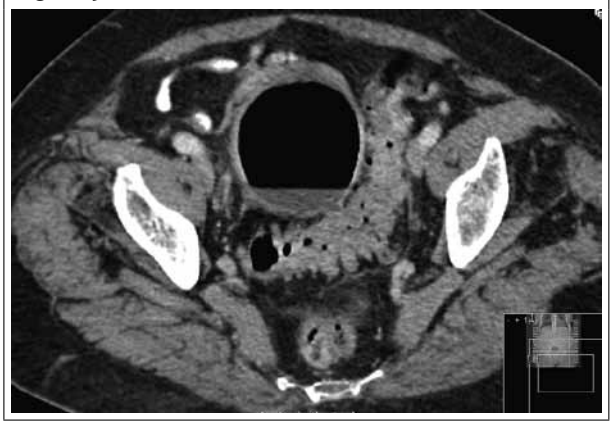
The typical appearance of GCD is a smooth-walled, air-filled oval or round structure on plain abdominal radiographs visible in 99% of the cases. An air-fluid level is frequently seen in an upright view.[1,3] As shown in this quiz case, unfamiliarity with this entity may cause the diagnosis to be missed. Confirmation of diagnosis is best achieved with CT, where a thick-walled air-filled cavity is found appending the colon.

Communication with the colon lumen can be demonstrated in 45 to 66% on barium enema through barium influx or expansion of the cyst on consecutive images.[4] Both colonoscopy and enema are relatively contraindicated because of risk of perforation.[1]

Other air-filled structures are giant duodenal diverticula, air in the gallbladder and in the urinary bladder, an abscess, a necrotising tumour or an isolated bowel segment in case of a volvulus. GCD can be differentiated from these entities based on morphology, location and clinical information.[5]

Risk of complications necessitates treatment. In most cases diverticulectomy or resection of a diseased colon segment is performed. Image-guided aspiration is indicated when immediate intervention is needed and surgery is not possible.[1,2]

Figure 3.



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SPECIAL ARTICLE

Dutch guideline for the management of hypertensive crisis – 2010 revision

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ABSTRACT

Hypertensive crises are divided into hypertensive urgencies and emergencies. Together they form a heterogeneous group of acute hypertensive disorders depending on the presence or type of target organs involved. Despite better treatment options for hypertension, hypertensive crisis and its associated complications remain relatively common. In the Netherlands the number of patients starting renal replacement therapy because of 'malignant hypertension' has increased in the past two decades. In 2003, the first Dutch guideline on hypertensive crisis was released to allow a standardised evidence-based approach for patients presenting with a hypertensive crisis. In this paper we give an overview of the current management of hypertensive crisis and discuss several important changes incorporated in the 2010 revision. These changes include a modification in terminology replacing 'malignant hypertension' with 'hypertensive crisis with retinopathy' and reclassification of hypertensive crisis with retinopathy under hypertensive emergencies instead of urgencies. With regard to the treatment of hypertensive emergencies, nicardipine instead of nitroprusside or labetalol is favoured for the management of perioperative hypertension, whereas labetalol has become the drug of choice for the treatment of hypertension associated with pre-eclampsia. For the treatment of hypertensive urgencies, oral administration of nifedipine retard instead of captopril is recommended as first-line therapy. In addition, a section on the management of hypertensive emergencies according to the type of target organ involved has been added. Efforts to increase the awareness and treatment of hypertension in the population at large may lower the incidence of hypertensive crisis and its complications.

KEYWORDS

Hypertensive crisis, guideline, management, hypertensive emergencies, hypertensive urgencies, renal sufficiency

INTRODUCTION

Hypertensive crises are a heterogeneous group of hypertensive disorders characterised by severe hypertension and acute target organ damage. As a result of better treatment possibilities for hypertension in the population at large it might be anticipated that the incidence of hypertensive crisis would decline. Yet hypertensive crisis remains relatively common in the Netherlands, especially among young and middle-aged adults of sub-Saharan African descent.[1] This is also substantiated by the number of patients in need of renal replacement therapy because of 'malignant hypertension'. Between 1990 and 2000 a total of 205 patients started renal replacement therapy in the Netherlands (1.6% of the total number of patients starting renal replacement therapy) because of malignant hypertension compared with 289 patients (1.7%) between 2000 and 2010.[2] This shows that although the relative contribution of renal failure attributable to malignant hypertension has remained unchanged, the absolute number of patients with renal failure as a result of malignant hypertension has increased by 40% in the past two decades. The observation that hypertension was not detected in half of the patients presenting with a hypertensive crisis implies that awareness and treatment of hypertension still needs to be improved, especially among young and middle-aged persons from sub-Saharan African descent. Next to

continuing efforts to improve the control of hypertension, the relatively high prevalence of hypertensive crisis and its associated complications suggest that appropriate recognition and management of hypertensive crisis remains important.

The 2003 guideline on the management of hypertensive crisis was published with the aim to provide a standardised evidence-based approach for the treatment of patients with hypertensive crisis in the Netherlands.[3] Recently, the 2003 guideline on hypertensive crisis was updated. The scope of this paper is to give an overview of the current management of hypertensive crisis and to discuss several important changes included in the 2010 revision.

METHODS

In 2008, the Netherlands Society of Internal Medicine formed a working group to update the 2003 guideline on hypertensive crisis. A systematic search for articles on the management of hypertensive crisis was performed using Medline and the Cochrane Database (for a detailed description of search terms see the full version of the guideline). Literature was qualitatively assessed using standardised methods.[4] The result of the literature review was discussed during three working group meetings. After internal consensus, a concept version of the guideline was sent for internal and external review. A final version was approved by the members of the Netherlands Society of Internal Medicine on 18 November 2010. The definitive version of the revised guideline can be retrieved at www.internisten.nl/home/richtlijnen/definitief.

DEFINING HYPERTENSIVE CRISIS

In the literature, hypertensive crises are uniformly differentiated in hypertensive urgencies and hypertensive emergencies.[5] A hypertensive emergency refers to a situation where uncontrolled hypertension is associated with acute target organ damage to the brain, heart, kidney, retina or blood vessels, whereas a hypertensive urgency is used to denote the presence of uncontrolled hypertension without evidence of acute hypertensive organ damage. The diagnosis 'hypertensive urgency' may therefore be regarded as a diagnosis of exclusion. Although it is generally recognised that the rate of BP increase over time is more important for the development of acute organ damage than the absolute BP level, a hypertensive crisis usually develops when BP values exceed 120 to 130 mmHg diastolic and 200 to 220 mmHg systolic. In patients without pre-existing chronic hypertension, such as women with pre-eclampsia, a hypertensive emergency can develop at substantially lower BP values. Severe hypertension, defined as a BP between 180/110 mmHg and 220/130 mmHg without symptoms or acute target organ damage, is not considered a hypertensive urgency and is treated as a risk factor for cardiovascular disease.

HYPERTENSIVE EMERGENCIES

The diagnosis of hypertensive emergency is based on the presence of acute damage to the brain, kidney, heart, retina and blood vessels. Hypertensive emergencies are preferably treated with intravenous drugs on a ward with facilities for continuous haemodynamic monitoring such as a medium care, coronary care or intensive care unit. Patients with a hypertensive urgency can usually be treated with oral medication. The promptness of instituting medical therapy, type of medication and BP goal of a hypertensive emergency depends on the type of end organs involved. For example, a hypertensive crisis with acute congestive heart failure requires immediate BP reduction to (near) normal BP values (mean arterial pressure [MAP] 60-100 mmHg). Conversely, in patients with acute ischaemic stroke, immediate treatment is generally withheld. A summary of the treatment of hypertensive emergencies according to affected target organs is given in *table 1*. An overview of recommended drugs that are used for the treatment of hypertensive emergencies is listed in *table 2*.

Hypertensive crisis with retinopathy

Probably the most common type of hypertensive emergency is hypertensive crisis with grade III or IV retinopathy, where grade III points to the *bilateral* presence of flame-shaped haemorrhages of cotton wool spots, and grade IV to the presence of papilloedema. Apart from advanced retinopathy, microangiopathic haemolysis and renal dysfunction are frequently present.[6] The most common presenting symptoms and complications of hypertensive crisis with advanced retinopathy are listed in *table 3*. Labetalol, a combined α- and β-adrenergic-blocking drug, is preferred for the treatment of hypertensive crisis with retinopathy as it leaves cerebral blood flow relatively intact for a given BP reduction compared with nitroprusside.[7] Because of its long half-life (5.5 hours), hypotension may proceed after cessation of labetalol. In most cases, however, BP can be restored by intravenous administration of normal saline. Nitroprusside, nicardipine and urapidil, a combined α1-selective adrenoceptor blocker and 5HT agonist, can alternatively be used for this type of emergency.

Hypertensive encephalopathy

Hypertensive encephalopathy is present in 10 to 15% of patients presenting with hypertensive crisis and advanced retinopathy. However, vice versa, advanced retinopathy

Table 1. *Recommended treatment of hypertensive emergencies according to end organ involved*

	Time-line and target BP	1st line therapy	Alternative therapy	Recommended unit
Hypertensive crisis with retinopathy, micro-angiopathy or acute renal insufficiency	Several hours, MAP -20 to -25%	Labetalol	Nitroprusside Nicardipine Urapidil	Medium care/ ICU/ CCU
Hypertensive encephalopathy	Immediate, MAP -20 to -25%	Labetalol	Nicardipine Nitroprusside	ICU/ Medium care/ Stroke unit
Acute aortic dissection	Immediate, systolic BP <110 mmHg	Nitroprusside and esmolol	Labetalol	ICU
Acute pulmonary oedema	Immediate, MAP 60 to 100 mmHg	Nitroprusside (with loop diuretic)	Nitroglycerine Urapidil (with loop diuretic)	CCU/ICU
Myocardial ischaemia/infarction	Immediate, MAP 60 to 100 mmHg	Nitroglycerine	Labetalol	CCU
Acute ischaemic stroke and BP >220/120 mmHg*	1 hour, MAP -15%	Labetalol	Nicardipine Nitroprusside	Stroke unit/ICU
Cerebral haemorrhage and BP >180 systolic or MAP >130 mmHg	1 hour, systolic BP <180 mmHg and MAP <130 mmHg	Labetalol	Nicardipine Nitroprusside	Stroke unit/ICU
Acute ischaemic stroke with indication for thrombolytic therapy and BP >185/110 mmHg†	1 hour, MAP -15%	Labetalol	Nicardipine Nitroprusside	Stroke unit/ICU
Cocaine/XTC intoxication	Several hours	Phentolamine (next to benzodiazepines)	Nitroprusside	Medium care/ICU
Adrenergic crisis associated with pheochromocytoma or autonomic hyperreactivity	Immediate	Phentolamine	Nitroprusside Urapidil	Medium care/ ICU
Peri- and postoperative hypertension - during or after coronary bypass graft	Immediate	Nicardipine	Urapidil or nitroglycerine	Recovery or ICU
- during or after craniotomy	Immediate	Nicardipine	Labetalol	Recovery or ICU
Severe pre-eclampsia/eclampsia‡	Immediate, BP <160/105 mmHg	Labetalol (next to magnesium sulphate and oral antihypertensive therapy)	Ketanserin Nicardipine	Medium care/ ICU

MAP = mean arterial pressure; *for the treatment of patients with stroke we refer to the National guideline for the Diagnosis, Treatment, Therapy and Care for stroke patients, CBO 2008. †autonomic hyperactivity refers to a situation where hypertension is associated with endogenous catecholamine excess. Autonomic hyperactivity is observed in cases of clonidine-withdrawal, food products or medication that interact with monoamine-oxidase (MAO) Guillain-Barré syndrome, spinal cord injury and cerebral contusion; ‡for the management of patients with severe (pre)eclampsia, we refer to the guideline Hypertensive Disorders in Pregnancy of the Dutch Society of Obstetrics and Gynaecology (NVOG).

Table 2. *Overview of intravenous drugs for the treatment of hypertensive emergencies*

Drug	Onset of action	Half-life	Dose	Contraindications and adverse effects
Esmolol	1-2 min	10-30 min	0.5-1 mg/kg as bolus; 50-300 µg/kg/min as continuous infusion	2nd or 3rd degree AV block, systolic heart failure, COPD (relative); bradycardia
Phentolamine	1-2 min	3-5 min	1-5 mg, repeat after 5-15 min. until goal BP is reached; 0.5-1.0 mg/h as continuous infusion	Tachyarrhythmia, angina pectoris
Ketanserin	1-2 min	30-60 min	5 mg as bolus injection, repeat after 5 min (max 30 mg); 2-6 mg/h as continuous infusion	Prolonged QT interval, 2nd or 3rd degree AV block; bradycardia, hypokalaemia
Labetalol	5-10 min	3-6 hr	0.25-0.5 mg/kg; 2-4 mg/min until goal BP is reached, thereafter 5-20 mg/h	2nd or 3rd degree AV block; systolic heart failure, COPD (relative); bradycardia
Nicardipine	5-15 min	30-40 min	5-15 mg/h as continuous infusion, starting dose 5 mg/h, increase every 15-30 min with 2.5 mg until goal BP, thereafter decrease to 3 mg/h	Liver failure
Nitroglycerine	1-5 min	3-5 min	5-200 µg/min, 5 µg/min increase every 5 min	
Nitroprusside	Immediate	1-2 min	0.3-10 µg/kg/min, increase by 0.5 µg /kg/min every 5 min until goal BP	Liver/kidney failure (relative); cyanide intoxication
Urapidil	3-5 min	4-6 h	12.5-25 mg as bolus injection; 5-40 mg/h as continuous infusion	

Table 3. *Presenting symptoms and associated complications in patients with hypertensive crisis and advanced retinopathy*

	Percentage
Headache	63
Visual disturbances	59
Gastrointestinal symptoms (nausea, vomiting, weight loss)	49
Heart failure	30
Neurological sequelae (encephalopathy)	17
Left ventricular hypertrophy	86
Severe renal impairment (creatinine >300 μmol/l)	33
Mild to moderate renal impairment (115-300 μmol/l)	46
Microangiopathic haemolytic anaemia	28

may be lacking in up to 1/3 of patients.[8] Hypertensive encephalopathy is characterised by a reduced level of consciousness, delirium, agitation, stupor, seizures or cortical blindness in combination with a severe BP elevation. Focal neurological signs are uncommon and should raise the suspicion of an ischaemic stroke or cerebral haemorrhage. To verify the diagnosis additional CT or MRI imaging of the brain may be required. Cerebral oedema may be visualised as areas with increased signal density on MRI with T2 weighted or FLAIR imaging or as hypodense areas on CT or T1 weighted MRI imaging.[9,10] These areas are typically located in the posterior regions of the brain. The reason for this posterior predilection is likely the scarce innervation of the sympathetic nervous system in the supply area of the vertebral arteries resulting in a lower damping of BP oscillations as compared with the supply area of the carotid arteries. Hypertensive encephalopathy is also known as one of the causes of reversible posterior leucoencephalopathy syndrome (RPLS).[10] Besides hypertension, RPLS is also associated with thrombotic thrombocytopenic purpura (TTP), carotid endarteriectomy hyperperfusion syndrome, cytotoxic therapy (e.g. cyclosporine and tacrolimus) and administration of antiangiogenic and proapoptotic drugs, such as bevacizumab and bortezomib. In many of these situations hypertension is also present. Therefore, the cause of this syndrome appears to be multifactorial including, apart from hypertension, sudden increases in cerebral perfusion and endothelial damage. The cerebral white matter lesions that are observed on MRI imaging are in most cases reversible with timely institution of BP-lowering therapy and removal of other provoking factors (e.g. cytotoxic or antiangiogenic therapy).

In patients with hypertensive encephalopathy, antihypertensive treatment should be started immediately to lower BP in a controlled way in order to prevent further neurological deterioration and irreversible brain damage. Like hypertensive crisis with retinopathy, labetalol is preferred because cerebral blood flow is better preserved than with nitroprusside.[7] In case of seizures (temporary) anticonvulsant therapy should be instituted.[11] If neurological deterioration occurs during the initial BP-lowering phase the presence of a cerebral haemorrhage or ischaemic stroke should be considered. In these cases further BP lowering may adversely affect neurological outcome. Other causes for neurological deterioration are cerebral hypoperfusion caused by excessive BP reduction, nitroprusside toxicity and obstructive hydrocephalus due to compression of the cerebral aqueduct as a result of oedema.

Acute myocardial ischaemia or infarction

In patients with hypertensive crisis, the increase in afterload and myocardial oxygen demand may induce myocardial ischaemia. Oxygen supply may be further impaired by the presence of left ventricular hypertrophy decreasing coronary flow reserve.[12] In these patients therapy should be aimed at lowering BP without causing reflex tachycardia because this reduces diastolic filling time and increases myocardial oxygen demand. Both nitroglycerin or labetalol may safely reduce BP in patients with hypertension and acute myocardial ischaemia.[13,14] Additional β-blockade may be indicated for patients receiving nitroglycerin, especially if tachycardia is present. In comparison with nitroglycerin, sodium nitroprusside decreases regional blood flow in patients with coronary abnormalities and increases myocardial damage after acute myocardial infarction.[14-16] Urapidil may alternatively be used for the management of hypertensive crisis with myocardial ischaemia.[17,18]

Acute congestive heart failure

In patients with hypertensive crisis and acute congestive heart failure, nitroprusside is the drug of choice by its ability to immediately decrease ventricular pre- and afterload. Nitroglycerin may be a good alternative, although doses in excess of 200 μg/min may be required to achieve the desired BP-lowering effect. Compared with nitroglycerin, urapidil gives a better BP reduction and improvement of arterial oxygen content without reflex tachycardia.[19] Concomitant administration of loop diuretics decreases volume overload and helps to further lower BP.

Acute ischaemic stroke and cerebral haemorrhage

To limit the risk of acute hypertensive complications in patients presenting with ischaemic stroke, the BP is lowered if it remains >220/120 mmHg in the acute phase. In order to maintain perfusion of the penumbra and to prevent hypoperfusion of cerebral areas that suffer from impaired cerebral autoregulation, the goal is to lower MAP initially by no more than 15%.[20,21] In the event that an acute ischaemic stroke can be treated with thrombolytic therapy,

the BP needs to be lower than <185/110 mmHg. In case of an acute cerebral haemorrhage consensus dictates that systolic BP should be lowered to <180 mmHg and MAP <130 mmHg.[22] Whether a more vigorous BP-lowering strategy in the acute phase of a cerebral haemorrhage improves outcome is currently being studied in the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2). This trial started in 2008 and is expected to be completed in December 2011. For the management of hypertension in the acute phase of ischaemic stroke or cerebral haemorrhage labetalol is the drug of choice. If labetalol is contraindicated, nitroprusside and nicardipine are useful alternatives.

Acute aortic dissection

Patients presenting with an acute aortic dissection need immediate therapy to reduce BP to a systolic BP of 100 to 110 mmHg or the lowest tolerable value to prevent aortic rupture. To achieve a quick reduction in systolic BP without increasing heart rate, a combination of nitroprusside and esmolol – a rapidly acting β-blocking agent for intravenous use – or intravenous metoprolol is preferred.[23,24] Alternatively, bolus injections of labetalol can be used with the possible disadvantage that its long half-life prohibits immediate correction of BP in case of hypotension.

Adrenergic crisis

An adrenergic crisis refers to a situation where a hypertensive crisis is caused by endogenous (pheochromocytoma, clonidine withdrawal) or exogenous (XTC, cocaine or amphetamine abuse) excess of catecholamines. The treatment of choice includes either phenoxybenzamine, a non-competitive α-blocking agent, or phentolamine, a competitive α-blocking drug. In addition β-blocking agents can be added in case of tachycardia, but only after α-blocking therapy has been instituted. Next to phentolamine, both nitroprusside and urapidil are effective for the perioperative management of pheochromocytoma.[25,26] Labetalol has been associated with hypertensive bouts during surgery and is therefore less suitable for the treatment of pheochromocytoma during surgery.[27,28] In case of cocaine, XTC or other amphetamines, anxiolytic drugs are indicated first. Phentolamine can be added if hypertension persists after benzodiazepines have been given.[29] If myocardial ischaemia is present both nitroglycerin or verapamil can be used to induce coronary vasorelaxation.[30,31] To prevent secondary thrombosis resulting from ischaemia-reperfusion injury concomitant administration of aspirin is advocated.

Perioperative hypertension

Hypertension frequently complicates surgery either because of increased activation of the sympathetic nervous system (e.g. from pain or ischaemia), perioperative administration of vasoconstrictive agents, volume expansion or temporary cessation of BP-lowering drugs prior to the procedure. The risk associated with uncontrolled hypertension depends on the type of surgery, but is most prominent in patients subjected to cardiovascular surgery who are at risk of a vascular leak, or in patients who need brain surgery and are at risk of cerebral oedema as a result of an increase in intracranial pressure. Nicardipine, a calcium-blocking agent for intravenous use, is recommended for the treatment of postoperative hypertension after cardiac bypass surgery and for the treatment of BP during brain surgery. In case of tachycardia, β-blocking agents may be added to decrease myocardial oxygen demand.

Hypertensive crisis in pregnancy/ pre-eclampsia

In patients with severe pre-eclampsia or eclampsia, BP-lowering therapy is given next to administration of magnesium sulphate and/or labour induction. The consensus is to lower the BP <160/105 mmHg to prevent acute hypertensive complications (most notably cerebral haemorrhage) in the mother. Labetalol is the drug of choice if intravenous treatment is required.[32,33] Preferably, labetalol is combined with oral BP-lowering therapy consisting of α-methyldopa and nifedipine OROS to prevent foetal bradycardia. In any case, foetal heart rate should be monitored and the dose of labetalol should not exceed 800 mg/24 hours in the prenatal period. If labetalol is contraindicated or does not lower BP sufficiently, nicardipine can be used as an alternative.

HYPERTENSIVE URGENCIES

Hypertensive crisis without emergency symptoms can usually be treated with oral BP-lowering agents. Although evidence regarding the preferred time to reach goal BP and type of BP-lowering medication is limited, there is evidence that a steep decrease in BP, such as reported with sublingual nifedipine tablets, can lead to cerebral, cardiac and renal ischaemia.[34] Moreover, placebo-controlled trials have shown that BP decreases spontaneously in a substantial proportion of patients.

For hypertensive urgencies, the treatment of choice is oral nifedipine retard 20 mg. Sublingual nifedipine should be avoided because of the risk of uncontrolled hypotension. Other calcium blockers such as nifedipine OROS or amlodipine have a slower onset of action and are therefore less suitable for the treatment of a hypertensive urgency. Patients should be observed for at least two hours after taking nifedipine. BP should be measured with a maximal interval of 15 minutes between measurements. Before discharge, BP should be lower than <180/110

mmHg, but at least <200/120 mmHg. Although the risk is probably small, a steep or symptomatic decrease in BP can be treated with intravenous saline. Patients who are discharged should be seen by their general practitioner or at the outpatient department within three to five days for further treatment and analysis of their hypertension.

DISCUSSION

In comparison with the 2003 Dutch guideline on the management of hypertensive crisis several changes have been made. An outline of the most important changes incorporated in the 2010 revision is given in *table 4*.

In the 2010 revision the term 'malignant hypertension' has been replaced by 'hypertensive crisis with retinopathy'. The working group has decided on this change in terminology because the survival of patients with 'malignant hypertension' has considerably improved as a result of the advent of effective antihypertensive agents and renal replacement therapy. If, next to the presence of retinopathy, other target organs are involved they can be included to allow a more accurate description of this type of emergency which may also include hypertensive encephalopathy, microangiopathic haemolysis, pulmonary oedema and acute renal failure.

In line with other guidelines and the literature on hypertensive crisis, the working group has chosen to list patients with hypertensive crisis and retinopathy (with or without other signs of acute end-organ damage) under hypertensive emergencies in the revised guideline. Accidental lowering of MAP by >50% in patients with hypertensive crisis has been associated with an increased risk of ischaemic stroke and death.[35-37] In patients with hypertensive crisis and advanced retinopathy cerebral autoregulation is impaired,[38] putting them at risk of cerebral hypoperfusion when BP is lowered. In addition, the variations in volume status and renin-angiotensin system activation observed in patients with hypertensive crisis and advanced retinopathy may lead to unpredictable BP lowering responses.[39,40] Intravenous BP-lowering therapy allows controlled reduction of BP and minimises the risk of prolonged (unrecognised) hypotensive episodes. This means that patients with hypertensive crisis and retinopathy are preferably treated with intravenous drugs under continuous haemodynamic monitoring. Finally, hypertensive crisis with advanced retinopathy is frequently complicated by acute renal dysfunction suggesting that the ischaemic retinal lesions are a sign of ischaemic lesions within the kidney and elsewhere. Close BP monitoring and a timely response to excessive BP reductions may prevent further renal deterioration and facilitate recovery of renal function after the acute phase.

Table 4. *Most important changes included in the 2010 revision of the hypertensive crisis guideline*

1. Substitution of the term 'malignant hypertension' by hypertensive crisis with retinopathy
2. Classification of hypertensive crisis with retinopathy under hypertensive emergencies instead of hypertensive urgencies
3. Preference for nicardipine instead of nitroprusside or labetalol for the management of perioperative hypertension
4. Preference for labetalol instead of dihydralazine or ketanserin for the management of pre-eclampsia and hypertensive crisis in pregnancy
5. Preference for nifedipine retard instead of captopril for the treatment of a hypertensive urgency and limitation of the list of alternative BP-lowering agents

For the treatment of perioperative hypertension, the type of surgery and subsequent vulnerability of organs is important in determining the most suitable BP-lowering drug. In the revised guideline the management of perioperative hypertension has been adapted to the type of target organ involved. For coronary bypass surgery, BP should be lowered without compromising myocardial blood flow. Nicardipine appears to have a more favourable effect on maintaining stroke volume and myocardial perfusion than nitroprusside or nitroglycerin,[41,42] whereas urapidil and nicardipine are equally effective in maintaining myocardial function.[43] If hypertension complicates intracranial surgery, BP-lowering therapy should not increase intracranial pressure. Labetalol and nicardipine are equally effective in lowering BP without raising intracranial pressure.[44] In contrast, nitroprusside and urapidil have been shown to increase intracranial pressure during brain surgery and are therefore less suitable for this type of surgery.[45,46]

In the 2010 revision, labetalol has become the treatment of choice if intravenous therapy is required for the management of pre-eclampsia and hypertensive crisis in pregnancy. A meta-analysis of published randomised trials has shown that the use of dihydralazine is associated with adverse perinatal outcomes for both the mother and baby compared with labetalol, despite equal BP-lowering potential.[47] Ketanserin appears to be less effective in lowering BP, although it has been associated with a lower risk of HELLP syndrome in one study.[48] The choice for labetalol accords with the upcoming guideline of the Dutch Society of Obstetrics and Gynaecology on hypertension in pregnancy and the NICE guideline in the UK.[33]

When treating hypertensive urgencies, agents that have a rapid onset of action and predictable BP response with minimal side effects or contraindications are

preferred. Nifedipine retard lowers BP 15-30 minutes after intake with a maximal effect after 4-6 hours, whereas captopril has a maximal effect two hours after administration. Previous studies have shown that the BP response to dihydropyridine calcium antagonists such as nifedipine is relatively independent of volume status.[49,50] In contrast, the BP-lowering effect of ACE inhibitors (or other renin-angiotensin blockers) depends on intravascular volume status and activity of the renin-angiotensin system.[40] Because of the more gradual and predictable BP-lowering response of nifedipine and lack of contraindications for its use, the working group has changed its preference to nifedipine retard instead of captopril for the treatment of hypertensive urgencies whereas minoxidil and atenolol have been removed as a possible treatment option because of their slow onset of action and relative frequent occurrence of adverse effects.

PERSPECTIVES

Hypertensive urgencies and emergencies are a heterogeneous group of acute hypertensive disorders requiring prompt recognition and appropriate management to limit or prevent end-organ damage. In the 2010 revision, the working group has updated the evidence-based and, if evidence was lacking, reason-based approach towards the management of hypertensive crisis. Future research should be aimed at further delineating the discriminative value of diagnostic strategies in identifying patients at risk and by examining the optimal management of particular hypertensive urgencies and emergencies, especially with regard to the effectiveness and safety of oral medication. Despite the widespread availability of cheap and effective BP-lowering drugs, the incidence of hypertensive crisis has failed to diminish in large urban communities, especially among patients from sub-Saharan African descent. More importantly, the nationwide number of patients starting dialysis as a result of hypertensive crisis has increased in the past two decades. These complications are potentially preventable by timely recognition and treatment of hypertension, especially in young and middle-aged adults who are considered at low cardiovascular risk. Increased awareness and treatment of hypertension, also in persons who are otherwise considered at low cardiovascular risk, may decrease the incidence of hypertensive crisis and its associated complications.

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LETTER TO THE EDITOR

Comment to case report on eosinophilic gastroenteritis

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The case report by Verheijden and Ennecker-Jans on eosinophilic gastroenteritis[1] is highly appreciated. We would like to add a word of caution in view of the potential dangers of indiscriminate initiation of steroid therapy. It is necessary to exclude latent tuberculosis and strongyloides infection in subjects at risk.[2-5] Travel history, insufficiently treated infections and abnormalities on the chest X-ray may be indicative. Reactivation of tuberculosis and strongyloides hyperinfection syndrome may lead to life-threatening complications. Clinical symptoms and radiographic findings are characteristically atypical; peripheral blood eosinophilia can be absent in strongyloides hyperinfections.

Testing prior to initiation of immunosuppressive treatment preferably by interferon-γ release assays (IGRAs)[6,7] and strongyloides serology is easy and highly sensitive.[5]

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