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Blue-grey skin discoloration and dark urine; what is your diagnosis?

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EDITORIAL

Seen from the moon we are all the same size: Deceased donation in the Netherlands

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Kidney transplantation is a life-saving therapy for patients with end-stage renal disease (ESRD). In addition to providing a survival benefit, it improves the quality of life and is also cheaper compared with dialysis.[1] However, in the Netherlands, as in the rest of Europe, there is a shortage of deceased organ donors and supply does not meet demand. This has spurred research to find ways to improve the quality and longevity of deceased donor organs. Examples of such strategies include machine preservation of organs and other interventions aimed at decreasing ischaemia-reperfusion injury.[2,3] In addition, the past decades have seen an increasing use of organs from deceased donors that were not considered for transplantation in the past.

Two types of deceased donors are distinguished: donation-after-brain death (DBD) and donation-after-circulatory death (DCD) donors.[4] The latter group was formerly known as non-heart beating donors and is divided into four different categories.[4] The majority of DCD donors in the Netherlands are of category 3. These are patients with an infaust medical prognosis (often because of irreversible neurological injury) who do not meet the brain death criteria and in whom the medical decision is made to withdraw life-supporting treatment. After circulatory arrest has occurred and after respecting a no-touch period of five minutes, the donor is transferred to the operating theatre for procurement of the organs.[4]

The results of DCD donor kidney transplantation are good. Although there is a higher risk of both primary non-function and delayed graft function, kidney allograft survival is not very different from DBD donor kidney transplantation.[5] Importantly, DCD donor kidney transplantation offers a survival benefit compared with dialysis.[6] In the Netherlands, a national DCD donor protocol is in effect and since 2001, kidneys from both DBD and DCD donors are indiscriminately allocated by means of the national renal allocation program.

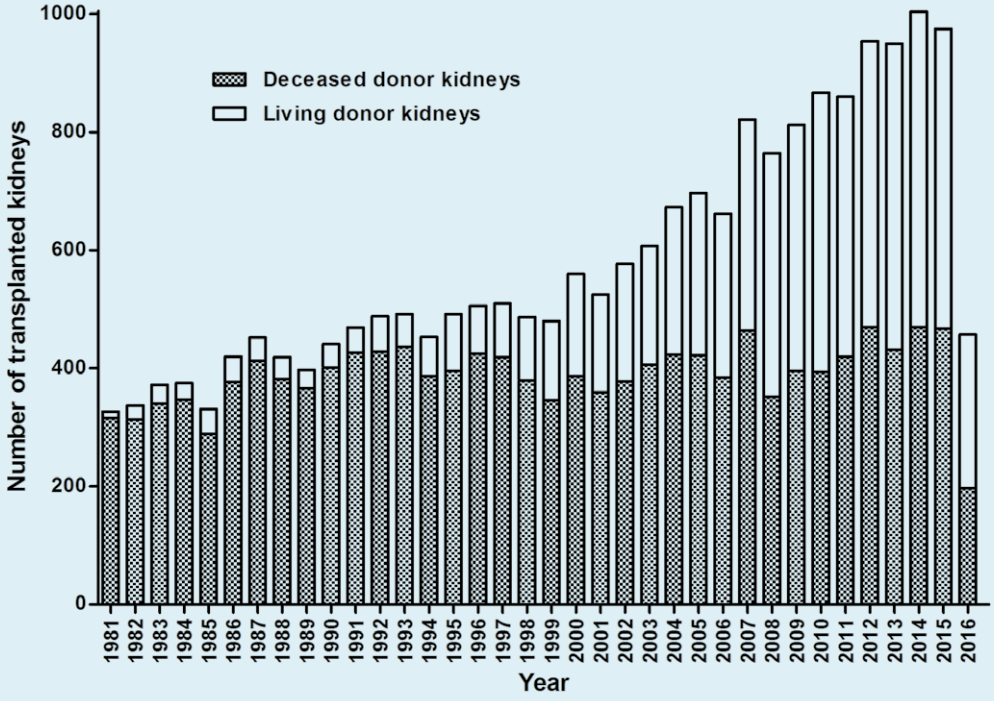
In this edition of the *Netherlands Journal of Medicine*, Leiden and colleagues report a study which investigated how the introduction of the Dutch national DCD donor program affected the overall number of referred and actual donors and the resulting transplantations in the period 2000 to 2014.[7] Their analysis demonstrates that the total number of donors (both DBD and DCD) that were referred for organ donation increased from 213 in the year 2000 to 336 in 2014, corresponding with an increase of 58%. During this same period, the number of organ transplantations increased by 42% and rose from 646 to 920. This increase in both referred and utilised donors largely resulted from the growth of the number of referred DCD donors, which represented 14% of all donors in 2000 and 54% in 2014.[7]

However, the number of DCD donors from whom organs were actually recovered and subsequently transplanted increased by only 34%. In addition, the utilisation rate of organs recovered from DCD donors decreased during the study period from 84% (2000-2002) to 67% (2012-2014). This probably resulted in part from the increase in age of DCD donors that occurred during this same time period.[7]

So is the glass half full or half empty? Obviously, the good news is that through the continued efforts of many, during the past 15 years, there has been a growth in the number of donors resulting in more patients having been transplanted. As such, the Dutch national DCD program, which aimed to create an extra pool of donors, has been very successful.

The downside may be that this growth has been realised by transplanting more organs from elderly DCD donors. The quality of such organs is less and graft survival not comparable to that of younger DCD donors. In addition, organs from many DCD donors were not procured after referral or the organs were not considered suitable after explantation. Thus, making a transplantation from a DCD donor possible requires more effort compared with a DBD donor. Third, the growth of the number of DCD donors may have resulted from a substitution of DBD donors. This is a real concern because the medical management

Figure 1. *Numbers of transplanted kidneys in the Netherlands from 1981 up until 6 July 2016. The annual number of deceased donor kidney transplantations (shaded bars) and the number of living donor kidney transplantations (open bars) are depicted*



of DBD donors is different from that of DCD donors and intensive care specialists may not wait for brain death to occur. If this is the case, DCD donation may put the cart before the horse.

Finally and perhaps most importantly, it remains to be seen whether the trend observed during the past 15 years and reported here will continue. Recent data from the Dutch Transplant Foundation (see www.transplantatiestichting.nl) demonstrate that the number of effectuated deceased donor transplants in the first months of 2016 has dropped as compared with the same period in 2015. Between 1 January and 6 July 2016, 111 deceased organ donors were effectuated compared with 134 donors in the same period in 2015, corresponding with a 17% decrease. The number of transplanted kidneys from DBD donors in the first half of 2016 was comparable with 2015, with 102 and 103 kidneys, respectively (-1%). The number of kidneys transplanted from DCD donors decreased by 27% from 130 (2015) to 95 (2016). It therefore appears that nothing much may have changed (*figure 1*).

So what are the therapeutic options for patients with ESRD? We believe the answer is an increasing use of living donor kidney donation. Living kidney donation, and preferably pre-emptive transplantation, is the preferred transplantation modality.[8] More than half of all kidney transplantations in the Netherlands is now performed with the use of living donors (see www.transplantatiestichting.nl and *figure 1*) It is the living kidney donor program which is largely responsible for the increase of the total number of kidney transplantations in the Netherlands and the decrease of the waiting list that has been observed in recent years.

It appears that there is room to increase the living donor program even further.[9] Kidney exchange programs, such as kidney paired donation with the use of kidneys from non-directed (or altruistic) donors in a national program, are likely to expand the live donor pool.[9] In addition, home-based patient education programs have been shown to increase patient's knowledge about renal replacement therapy (RRT), to change their attitude towards RRT, to optimise informed decision-making and to promote access to (pre-emptive) living donor kidney transplantation.[10,11] In 2016, four transplant centres and four large dialysis centres embarked on a project sponsored by Zorgverzekeraars Nederland (The Dutch Association of Health Insurers) entitled 'Nierteam aan Huis' (kidney team at home) to find out whether the results of this strategy can be generalised. However, for individuals who are waiting for a non-renal organ, the prospects are not so bright. Patients with end-stage liver or pulmonary failure have no alternative but transplantation and for patients with end-stage heart failure, transplantation is still the best treatment option.[12]

Many of these patients will die on the waiting list, will be removed from the waiting list or will not be listed at all because their chances of getting an organ transplant in time are slim. As transplant professionals, we owe it to these patients to keep the pressure on the general public and our politicians to increase the rate of organ donation in the Netherlands.

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ORIGINAL ARTICLE

Controlled donation after circulatory death in the Netherlands: more organs, more efforts

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ABSTRACT

Background: The Netherlands was one of the first countries in Europe to stimulate controlled donation after circulatory death (cDCD) at a national level in addition to donation after brain death (DBD). With this program the number of organ transplants increased, but it also proved to have challenges as will be shown in this 15-year review.
Methods: Data about deceased organ donation in the Netherlands, from 2000 until 2014, were analysed taking into account the whole donation process from donor referral to the number of organs transplanted.
Results: Donor referral increased by 58%, from 213 to 336 donors per year, and the number of organs transplanted rose by 42%. Meanwhile the contribution of cDCD donors increased from 14% in 2000 to 54% in 2014 among all referrals. The organs were transplanted from 92-99% of referred DBD donors, but this percentage was significantly lower for cDCD donors and also decreased from 86% in 2000-2002 to 67% in 2012-2014. In 16% of all referred cDCD donors, organs were not recovered because donors did not die within the expected two-hour time limit after withdrawal of life-supporting treatment. Furthermore, cDCD is more often performed at a higher donor age, which is associated with a lower percentage of transplanted organs.
Conclusion: Although cDCD resulted in more transplants, the effort in donor recruitment is considerably higher. Important challenges in cDCD that need further attention are the time limit after withdrawal of life-supporting treatment and donor age, as well as the possibilities to stimulate non-renal transplants including the heart by machine preservation.

KEYWORDS

Donation after circulatory death, organ donation, organ transplantation

INTRODUCTION

Organ donation after circulatory death (DCD), in addition to donation after brain death (DBD), is one of the ways to tackle the growing demand for organs for transplantation. The Netherlands was one of the first European countries to transplant organs (kidneys) from DCD donors, starting in the early 1980s.[1,2] DCD in the Netherlands is supported by legislation on organ donation and a national DCD protocol was introduced to standardise the DCD procedures. The majority of DCD donors in the Netherlands are controlled DCD. According to the Maastricht criteria (*table 1*) these donors are of category 3 (cDCD3), patients with an infaust medical prognosis, where treatment will be withdrawn awaiting circulatory arrest.[3] Since February

Table 1. *Categories of donation after circulatory death according to Maastricht criteria**[3]

Category I donors are dead on arrival at the hospital
Category II donors have undergone unsuccessful resuscitation
Category III donors are those who are expected to go into cardiac arrest
Category IV donors were brain dead when their heart arrested

*categories 1-4 that are used as suggested by the DCD-congress of Maastricht in 1995; categories I and II are also named uncontrolled DCD and categories III and IV are controlled DCD; the original term non-heart-beating donation was changed to donation after circulatory death in the last decennium.

2001, kidneys from both DBD and DCD donors have been indiscriminately allocated through the standard national renal allocation program. Although there is a higher risk for primary non-function or delayed graft function after cDCD kidney transplantation, the small difference in graft survival after cDCD compared with DBD kidney transplantation turned out to be acceptable.[2,4,5]

In practice, patients in intensive care units (ICU) with a non-recoverable or irreversible neurological injury, not meeting brain death criteria, in whom the medical decision to withdraw treatment is taken, are candidates for cDCD and can be referred to the organ procurement organisation. According to the Dutch protocol, cDCD is possible when there is an expected time between withdrawal of life-supporting treatment and circulatory arrest (agonal phase) of two hours or less for kidneys and one hour or less for liver, lungs and pancreas. During this time the organ procurement team is stand-by. After circulatory arrest a no-touch period of five minutes is maintained after which the donor is transported to the operating theatre to procure the organs.

Although the cDCD program predominantly concerned kidney transplantation, the Netherlands has also been successfully transplanting livers from DCD donors since 1999, and DCD lungs and pancreas since 2005.[2,6,7] The question raised by the increasing number of DCD donors is how it affects the donation program in terms of effort and number of renal as well as non-renal transplantations. In this article we describe 15 years of experience, between 2000 and 2014, of cDCD in the Netherlands, starting with the number of organ donors who entered into the deceased donation program (referred donors). We focussed on the number of donors from which no organ was recovered or transplanted after referral and which limitations were encountered in cDCD donation. Finally we show the effect on the number of transplantations.

METHODS

We extracted data regarding deceased organ donation and transplantation in the Netherlands, during the years 2000-2014, from the organ donor procurement registration of the Dutch Transplant Foundation. First we evaluated the total number of referred DBD, cDCD (Maastricht category 3 and 4) and uncontrolled DCD (Maastricht category 1 and 2) donors per year. Referred donors are defined as potential donors in whom at least one organ is reported to the organ procurement organisation with the intention to donate.

From the referred DBD and cDCD3 (Maastricht category 3 only) donors we calculated the percentage of donors whose organs were recovered for transplantation (actual donors) and the percentage of donors from whom at least one organ was used for transplantation (utilised donors, see *figure 1*). These calculations were done per three-year periods, in order to avoid fluctuations that are present in analyses per year. Reported reasons for no procurement or no transplantation of organs were evaluated. We also analysed these numbers for different age groups. The numbers of transplanted DBD and DCD organs from Dutch donors were expressed per organ type, in which paired organs (kidneys and lungs) were counted as two. The mean number of organs transplanted per referred donor for cDCD and DBD donors were compared per year, with paired organs and split livers being counted as two. Differences in percentages of utilised donors between DBD and DCD, time periods, and age groups were statistically tested by chi-square test using IBM SPSS23 software.

To collect more information about the reasons for not procuring organs in cDCD donors after referral, we used data from another application, our national medical record review. In this application donation officers and transplant coordinators enter data from all patients who died in the ICU regarding organ donation, from identification of potential organ donors until organ procurement.[8] The database is almost complete for the years 2008-2014, covering 90% of all 1045 referred cDCD donors in the Netherlands in 2008-2014. From 941 referred potential cDCD donors in this period who gave consent for donation, we evaluated the reasons for not procuring the organs.

RESULTS

Donors

The total number of deceased patients in the Netherlands who were referred for organ donation increased by 58%, from 213 donors in 2000 (13.4 per million population) to 336 donors (20.0 per million population) in 2014 (*figure 2*). While DBD donor referral fluctuated between 111 and 170 donors (mean 137 donors) per year, cDCD donor

Figure 1. *Terminology in organ donation*

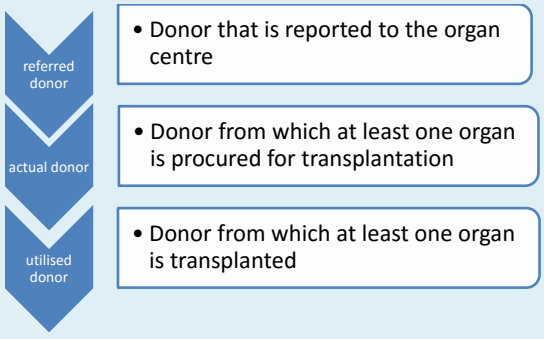
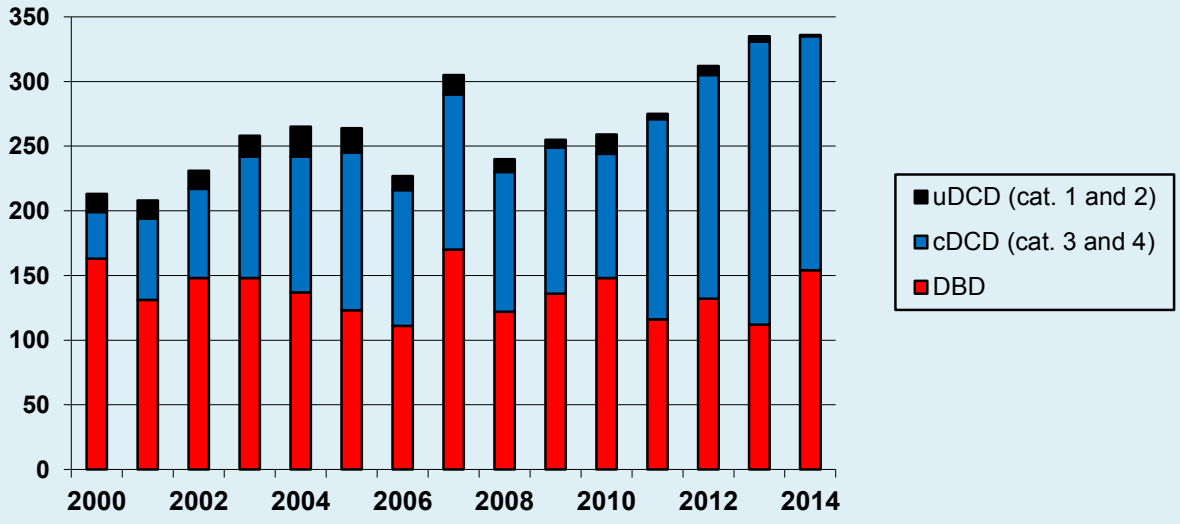


Figure 2. *Number of deceased organ donors from the Netherlands who were referred to the Dutch Transplant Foundation, per type* of donor, per year*



*uDCD (1-9% of all deceased donors yearly): uncontrolled donation after circulatory death; consists of Maastricht category 1 donors (died outside the hospital) and of Maastricht category 2 (unsuccessful resuscitation); cDCD: controlled donation after circulatory death; consists of Maastricht category 3 (awaiting cardiac arrest) and of Maastricht category 4 (cardiac arrest after brain stem death; nine donors in 15 years)

referral has grown from 36 to 181 donors yearly in these 15 years. This represented a change in the percentage of cDCD among all donor referrals of 14% in 2000 to 54% in 2014.

The total numbers of actual and utilised donors did not keep up with the numbers of donors referred, and increased less, at 34% for both. Over the past 15 years, the percentage of referred organ donors that became actual or utilised donors was significantly lower in cDCD3 than in DBD ($p < 0.001$). In DBD this utilisation rate fluctuated per three-year period between 95% and 97%, but it decreased in cDCD3 from 84% in the years 2000/2002 to 67% in 2012/2014 ($p < 0.001$, *figure 3*). Because the contribution of cDCD3 donors among deceased donors rose, the total percentage of utilised donors dropped in the Netherlands, from 95% in 2000 to 81% in 2014.

The number of cDCD3 donors predominantly increased in the higher age groups in recent years, especially since the donor age limit for DCD was raised from 65 to 75 years nationwide in the year 2011 (*figure 4A*). However, organs were less often recovered and transplanted from the older age groups of referred cDCD3 donors (*figure 4B*). The percentage of utilised donors was 86% in donors aged 0-40 years in contrast to 62% in donors aged 66-75 years ($p < 0.001$).

Reasons of non-procurement

Medical reasons were predominantly reported as the reason for not procuring organs from referred donors. After procurement, organs were not transplanted because of newly discovered medical reasons or anatomical pathology of the organ.

Our medical chart review database of potential donors who died in the ICU between 2008 and 2014 also showed another reason for non-procurement. In 71% of the 941 referred potential cDCD donors with consent for donation the organs were recovered. In 16%, procurement was not possible because donors did not die within the maximum two-hour time limit interval after withdrawal of life-supporting treatment (*figure 5*). In 10% of the referred cDCD donors, organs were not recovered because of other medical reasons that appeared after referral (for example abnormal features in organs discovered by imaging or lab).

Transplantations

Thus far the introduction of cDCD3 in the Netherlands has been successful. The number of referred donors rose considerably (58%, *figure 1*) and the total number of organs that are finally transplanted increased by 42%, from 646 in 2000 to 920 in 2014. The number of transplanted kidneys was higher during the years 2012-2014, compared with the three-year periods before 2012, and the numbers of transplanted livers and lungs steadily grew, all due to cDCD3 (*figure 6*). However, so far this has not resulted in higher numbers of transplanted organs per referred DCD donor. These numbers fluctuated yearly with between 1.6 and 2.0 organs per donor, numbers that are still lower than in DBD donors (varying between 3.3 and 4.1 organs per

Figure 3. *A. Percentage of actual and utilised donors among referred DBD donors per three-year period. B. Percentage of actual and utilised donors among referred cDCD3 donors per three-year period*

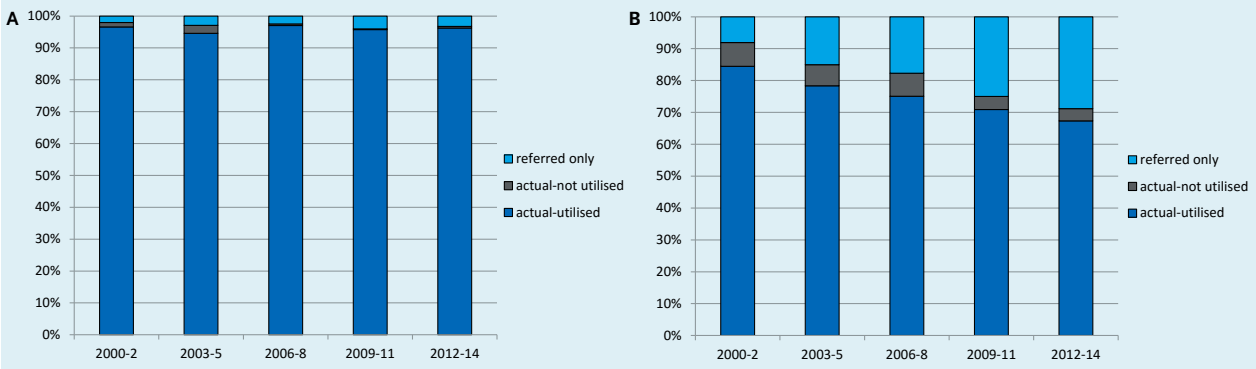
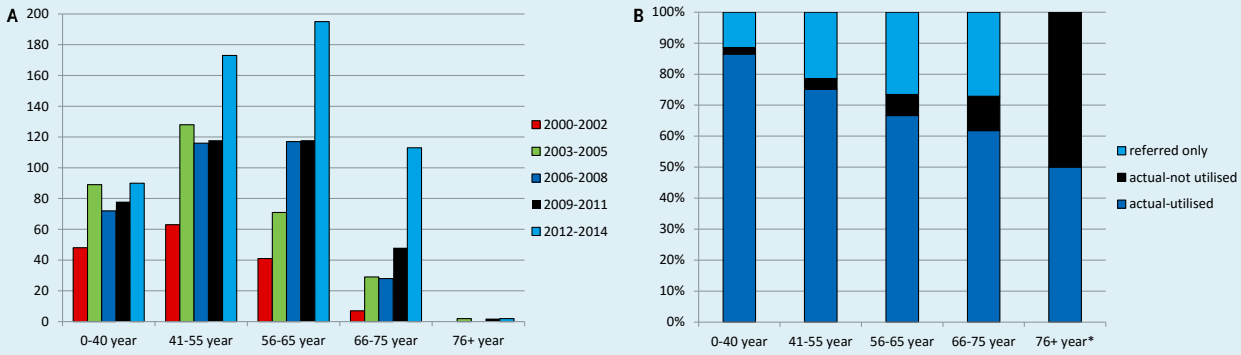


Figure 4. *A. Number of referred cDCD3 donors per age group in three-year periods. B. Percentage of actual and utilised donors among referred cDCD3 donors per age group*



*the age group of 76 years or older consisted of only six referred donors.

referred donor). cDCD still results predominantly in kidney donation and less often in non-renal donation (liver, lung, pancreas). And until now no DCD heart donation has been performed in the Netherlands.

DISCUSSION

The DCD program in the Netherlands was initiated to stimulate the total number of organ transplants from deceased donors by creating an extra pool of donors.[1] In the last 15 years, the referral of deceased Dutch organ donors increased significantly (58%), mainly because of cDCD. However, the number of actual and utilised cDCD donors, as well as the total number of organs transplanted, increased less impressively as compared with the number of donors referred. Thus much more effort is needed to stimulate the number of transplants by cDCD donation. Although the number of cDCD livers and lungs is growing, cDCD still results in less non-renal transplants than DBD and as yet heart transplants in the Netherlands.

Developments in the Netherlands regarding cDCD are comparable with those in the United Kingdom (UK) where cDCD has been widely introduced into the donation program. In the UK the number of donors increased by 64% (from 709 to 1164 donors) during the years 2003-2012, which was predominantly the result of the cDCD group growing from 9-43% of all donors.[9] Also

Figure 5. *Procurement of referred cDCD3 donors from ICUs during 2008-2014 and reasons of non-procurement*

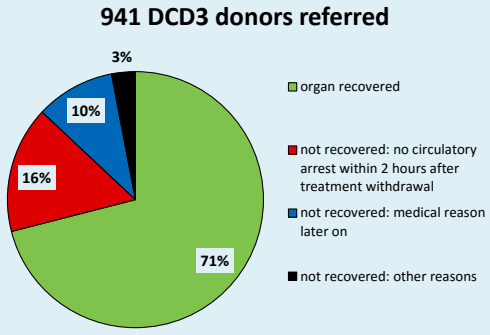
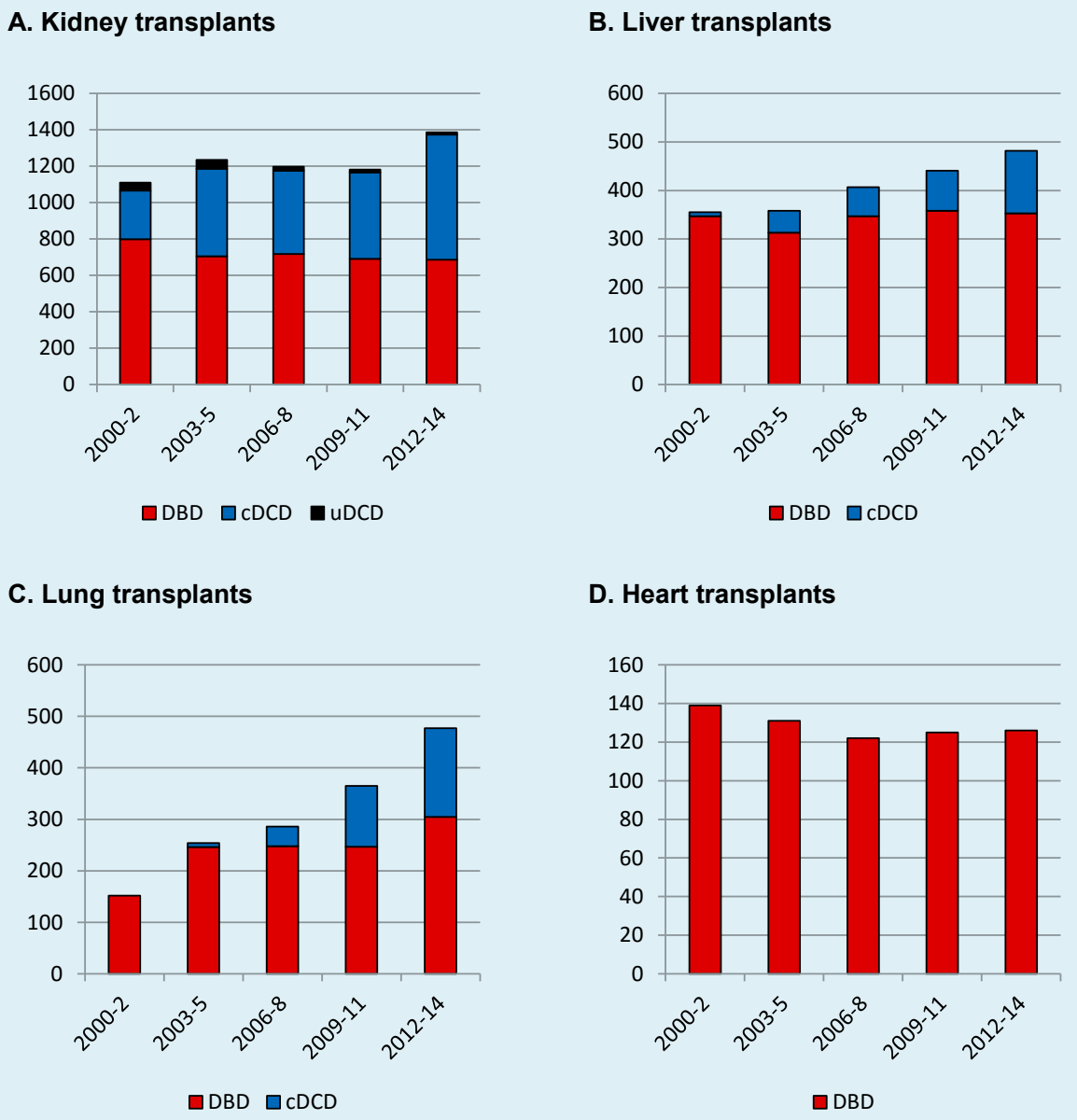


Figure 6. *Number of transplanted organs* from Dutch donors (DBD and DCD) per three years*



*paired organs (kidney or lung) and split livers are counted separately.

in the UK there is a discrepancy between the number of referred and transplanted organs from deceased donors. In the UK it was shown that considerably more DCD donors did not result in any organ transplantation after procurement as compared with DBD donors (14% vs. 2% in 2012). Furthermore the proportion of DCD kidneys that were recovered, but not transplanted, grew from 8% to 17% during the years 2003-2012, without any further reasons mentioned.[9] A similar development was seen in the Netherlands where an increasing number of referred DCD3 donor organs were not transplanted, even not procured (*figure 3B*).

In previous studies we reported that an initial higher number of cDCD until 2005 was consistent with a simultaneous lower number of DBD and we postulated the possibility of a 'substitution' instead of expansion of the donor pool by DCD.[10,11] A similar trend after introduction of DCD was suspected in the UK and to a lesser degree in the United States (US) and in Belgium.[2,12,13] It was suggested that potential DBD donors might be recovered as DCD, because of a change in the management of patients with severe brain injury, such as craniostomy, cooling of the patient or possible earlier referral for donation. Summers et al. suggested, however, that the large majority of DCD

donors could not originate from potential DBD donors, because the total number of patients who were possibly brain dead had decreased as well.[14] This was shown in potential donor audits in the ICU in the UK during 2004-2009. In the US the growing numbers of cDCD donors did not parallel the decrease in DBD donors, but the DCD numbers remained relatively small.[15] However, in a hospital region in the US that had relatively more DCD donors, up to 60% of all deceased donors, the number of DBD donors had decreased.[12] In Belgium cDCD particularly rose after the year 2005, but it did not increase the total kidney donor rates until 2010.[13] The possibility that a further growth in the number of cDCD donors in the Netherlands will be accompanied by a simultaneous decline in the numbers of DBD donors, with as a result less non-renal organs (especially no hearts), is still a matter of concern. cDCD donation is a valuable addition to the donor pool under the condition that it does not substitute the potential DBD pool. We therefore have to stimulate an attitude in hospitals to first wait for brain death determination. The growing number of liver and lung transplants from DCD donors is one of the reasons why the increasing percentage of cDCD donors has not dramatically disturbed the non-renal transplant programs so far, with the exception of heart transplantations, which are still fully dependent on DBD donations in the Netherlands. Also alternative opportunities to create an additional pool of deceased donors should be further explored, such as by stimulating referral of the number of uncontrolled DCD donors (Maastricht category 1 and 2) that cannot interfere with DBD or by stimulating donation from older DBD donors (aged 75 or older).

There are some more limitations to DCD that are responsible for relatively less transplants compared with DBD. One limitation is the warm ischaemia time, which is unavoidable after cessation of treatment in cDCD until death confirmation. The Netherlands has chosen a maximal time limit after withdrawal of life-supporting treatment of two hours for kidney donation and one hour for other organs. This study showed that of the referred cDCD donors, 16% did not die within this two-hour time limit.

In correspondence with our study, Wind et al. showed that 17% of cDCD donors did not die within two hours, and 24% not within one hour after withdrawal of life-supporting treatment. Among these Dutch potential DCD donors median time to death was 20 minutes, but time to death ranged from one minute to 3.8 days.[16] Comparable numbers were reported by Saidi et al. and Davila et al., who reported that 30% and 27%, respectively, of intended cDCD donors did not progress to circulatory arrest in one hour after withdrawal of life-supporting treatment.[12,17] There are ways to tackle this limitation in cDCD. Reid et al. reported that longer times after withdrawal of life-supporting treatment were associated with greater donor instability, but they also reported that neither patient instability nor its duration influenced kidney transplant outcome.[18] According to this group, it would be worthwhile to extend the waiting time to four hours as they showed that DCD kidney numbers increased by 30%. UK has recently introduced a maximal waiting period of three hours for abdominal teams.[19] But it is also known that the point at which cardiac arrest is reported is not clearly defined. While some hospitals define cardiac arrest as cessation of cardiac contraction, other hospitals choose for cessation of electrical cardiac activity.[19] So it is important to use universal definitions to evaluate a change in this waiting time properly. On the other hand we could use models to better predict the agonal phase after withdrawal of life-supporting treatment in potential cDCD donors.[16,17,20-22] This could prevent starting a laborious intensive and expensive donation procedure, involving transplant coordinators, procurement teams, and preparation of an operation room. It could also prevent a stressful time for a grieving family and disappointment due to an unsuccessful donation procedure.[23,24] Although it is hard to find a valid model based on risk factors that will be accurate enough to increase transplantation after donor referral, it is absolutely necessary to continue this research. According to our medical record review data from 2008-2013 another 615 ventilated patients from the ICU had a non-recoverable or irreversible medical status, not meeting brain death criteria, but they were not expected to die within two hours and were even not referred as potential cDCD donors. Some of them could have been donors using an extended waiting time after withdrawal of life-supporting treatment of up to four hours or by using an effective prediction model.

Another limitation in cDCD is that organs from older referred donors were less often transplanted, while especially the referral of older cDCD donors has grown in recent years. This could explain why the proportion of utilised donors in cDCD, which is already smaller as compared with DBD donors, has further decreased in recent years. One might expect that older donors are indeed more often discarded because of poor kidney function or proteinuria. However, we have no information about the exact medical reason for non-procurement.

Also follow-up analysis after transplantation of renal as well as non-renal organs from DCD donors needs to be continued. Analysis of kidney transplantations in the Netherlands has shown significantly decreased survival rates in grafts from DCD3 donors (85.0%) compared with those from DBD donors (93.7%) within the first three months after transplantation.[4] However, at 12 months, graft survival still differed by 9% between these groups (83.0% and 92.0%, respectively ($p < 0.03$)) in favour of DBD.

A solution to stimulate the number of organs suitable for transplantation from DCD donors, especially with respect to older marginal donors, is the improvement of donor management and introduction of new preservation techniques after procurement, such as normothermic regional perfusion and machine perfusion. With respect to kidney and lung donation, developments in this area are promising in the Netherlands.[25,26] Recent developments in DCD3 in Australia even show that heart donation is possible by using an ex-vivo Organ Care System machine.[27,28] It will be a new challenge to introduce DCD3 heart donation in the Netherlands as well as to shorten the heart waiting list.

In summary this study showed that a nationwide introduction of cDCD requires more efforts in donor activities and combatting limitations to reach more transplantations. More DCD has to be evaluated with care in the coming years, since a further rise in organs that are not transplanted will put pressure on resources, the potential willingness of professionals to invest time and money. Furthermore, it would be hard to explain the fact that organs are declined to the general public.

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DISCLOSURES

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ORIGINAL ARTICLE

Willingness to accept chemotherapy and attitudes towards costs of cancer treatment

A multisite survey study in the Netherlands

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ABSTRACT

Background: In the past years, interest in patient treatment preferences is growing. Our objectives were: (1) to assess and compare the minimal required benefit for patients with cancer, patients without cancer and healthcare professionals to make chemotherapy acceptable and (2) to obtain insight into attitudes towards societal costs of cancer treatment.

Patients and methods: We performed a prospective survey consisting of hypothetical scenarios among patients with cancer, patients without cancer and healthcare professionals. Participants were asked to indicate the minimal desired benefit in terms of chance of cure, life prolongation and symptom relief which would make intensive and mild chemotherapy regimens acceptable. In two other scenarios, attitudes towards monthly costs for chemotherapy treatment were examined.

Results: The minimal benefit required to make chemotherapy acceptable did not differ between cancer and non-cancer patients, with respect to chance of cure (mean 57%), life prolongation (median 24 months) and symptom relief (mean 50%); healthcare providers were likely to accept the same chemotherapy regimen at lower thresholds ($p < 0.01$). Education level was an important explanatory variable and the differences between patients and healthcare professionals disappeared when corrected for education level. Opinions about the maximum acceptable costs for chemotherapy displayed a large spread between the groups.

Conclusions: Minimal benefits to accept chemotherapy were not different between cancer and non-cancer patients, but are beyond what can generally can be achieved. Healthcare professionals were willing to accept chemotherapy for less benefit. This difference may be attributed to a difference in education level between the groups. Healthcare professionals rated the maximum acceptable societal cost for chemotherapy lower than patients.

KEYWORDS

Treatment preferences, decision-making, willingness to pay, chemotherapy, costs-valuation

INTRODUCTION

While chemotherapy for the treatment of cancer is expected to bring an overall benefit, it may also be associated with significant side effects. An optimal treatment is an individual decision which may result from the interaction between physician and patient. Many patients prefer and endorse shared decision-making with their physician.[1,2] During decision-making both parties should carefully weigh the relative harms and benefits of chemotherapy.

Understanding treatment preferences is essential for optimal decision-making. While some patients try

intensive treatments that are unlikely to help, others avoid mild treatments that may cure.[3] The healthcare professionals' view on the impact of treatment on patients' quality of life may differ from the patients' view in this respect. Therefore, it is important to obtain insight into both patients' and physicians' attitudes towards chemotherapy.

Various strategies are available to assess preferences for cancer treatments.[4] A pivotal British study assessed attitudes to chemotherapy by designing hypothetical scenarios with intensive and mild treatment regimens.[5] Participants were asked to rate the minimal benefit to make therapy worthwhile in terms of possibility of cure, survival gain and symptom relief. Several studies based their questionnaire on this classic method. Bremnes et al. repeated a comparable study in Scandinavia and in a study by Extermann et al. differences in preferences between French and American cancer patients were determined.[6,7] A review of international published literature showed that the treatment benefit that patients desire is small; however, the variance in preferences within studies is large.[8] Little is known about preferences for cancer treatment in the Netherlands. In the past two decades, a few Dutch studies were performed examining treatment preferences and decision-making.[9-12] Most of these studies focused on specific cancer types in a curative/adjuvant setting. For example, Jansen et al. examined preferences for adjuvant chemotherapy in early-stage breast cancer.[10] Breast cancer patients, who were about to start with and without chemotherapy, were asked to indicate the minimal benefit to make adjuvant chemotherapy acceptable. Patients with chemotherapy accepted therapy for significantly less benefit than their counterparts without chemotherapy. Generally, most of these Dutch studies focused on specific cancer types in a curative/adjuvant setting.

The negative aspects of anticancer therapy are not limited to the physical side effects for individual patients, but also include the costs of therapy. Costs of cancer care are high and expected to rise worldwide, thereby forcing decisions by healthcare policy makers. The annual costs for cancer care in the Netherlands have increased from €3.4 billion in 2007 to €4.8 billion in 2011, of which 9.8% was spent on drugs.[13] This upward trend is a result of factors such as the introduction of new medical technology for specific individual cancer treatment, the development of new anticancer therapies, the extension of cancer care and the ageing population.[14] In the majority of cost-analysing studies participants are asked to bid for a treatment by using bidding game strategies.[15,16] However, in countries with an advanced integrated healthcare system, the personal financial contribution is minimal. Therefore, it is more interesting to focus on public opinion towards capacity of insurances and the societal costs in cancer care.

The aim of this study was to determine cancer patients', non-cancer patients' and healthcare professionals' desired minimal benefits to make a chemotherapy-based treatment worthwhile, and to examine the degree of involvement during decision-making. A secondary objective was to assess attitudes towards cancer costs. In this article we report the data of a written survey that was performed among patients, with and without cancer, and healthcare professionals in the Netherlands.

METHODS

Design

The study design was a multisite prospective survey, performed by the Radboud University Medical Centre (Radboudumc) Nijmegen in collaboration with the teaching hospital Medisch Spectrum Twente (MST) Enschede, the Netherlands. The survey was performed between June and November 2013.

Questionnaire

The questionnaire assessed three main areas: questions directed to (1) treatment preferences and decision-making, (2) attitudes towards costs of cancer therapies and (3) information on demographics and the type of malignancy. Implementation of the survey was completely anonymous. When conducting this study no identifying information was collected from the participants.

Questions about preferences for chemotherapy were comparable with the original format designed by Slevin et al.[5] The original questions were translated into Dutch. In order to make the questionnaire easy to read we modified the layout into visual attributes. Two hypothetical chemotherapy-based scenarios were described along with their risks and side effects: an intensive toxic and mild regimen respectively. The intensive regimen described chemotherapy with a high risk of side effects and a higher risk of infections, bleeding complications and hospitalisation. The mild regimen described a chemotherapy schedule with less risk and side effects. Subjects were asked to rate their desired minimal benefit to make therapy acceptable in terms of probability of cure, life prolongation and cancer symptom relief. Alternatives ranged from 0 to 100% and from 0 to 60 months, respectively.

Attitudes towards cancer costs (not restricted to chemotherapy) were examined using willingness to pay-like questions. As it is not common for Dutch people to pay out-of-pocket for healthcare, we used a simplified payment scale of Mitchell and Carson.[17,18] Participants were asked to indicate the maximum cost – covered by healthcare insurance – for a novel treatment that only

prolongs survival by an extra three months. This question was incorporated into two hypothetical patient-based scenarios, one describing a cancer patient with a poor performance state and another describing a patient with a good performance. Costs were arranged from €2000 to more than €50,000 per month.

The last area focused on demographic factors including age, sex, education level, race or ethnic group, marital status and gross annual household income. Participants' preferred involvement in decision-making was determined using a translated Control Preferences Scale (CPS). The CPS is a validated and widely used scale containing five levels of participation in decision-making.[19] Cancer patients were also asked about disease-specific characteristics, such as cancer type, treatment intent, presence of metastases and duration of treatment. With regard to anonymity, no additional information was searched to validate the patient's perception about these characteristics.

According to Eurostat, the statistical office of the European Union, a new questionnaire should be tested at least once with potential respondents.[20] Therefore, two pilots were carried out to test the applicability of the questionnaire. Cancer patients (n = 25) and medical students (n = 18) were asked to critically assess the questions. Ultimately, based on our observations and their comments, we redesigned our final questionnaire.

Data collection

The population of this study consisted of three main groups: (1) patients currently on treatment for cancer, (2) patients without cancer, and (3) healthcare professionals. All included subjects were 18 years and older, and had a sufficient understanding of the Dutch language.

Between June and November 2013, 163 cancer patients who attended the Radboudumc and MST for outpatient chemotherapy or targeted therapy were asked to complete the questionnaire. Cancer patients who received hormonal therapy only were excluded. A total of 101 subjects without cancer were approached at the department of endocrinology (MST) and at the department of orthopaedics (Radboudumc). Patients were informed in person about the study intent, and were then asked to participate. To avoid external influences, participants were asked to complete the questionnaire individually.

In the same period, 400 healthcare professionals (physicians, primary care physicians and nurses), currently working in healthcare, received the questionnaire with an envelope for return and a link for online answering. The group of professionals consisted of either oncological or non-oncological medical specialists and nurses from both hospitals.

The response rate among cancer and non-cancer patients was 90.2% (n = 147) and 87.1% (n = 88), respectively. Among healthcare professionals, this rate was 44%, with 10.2% (n = 18) using the Internet to answer the questions. In total 35 questionnaires were excluded from data analysis because of incompleteness (n = 19) or because control patients or professionals reported a history of cancer (n = 16). Finally, 382 questionnaires (139 cancer, 82 non-cancer and 161 healthcare professionals, respectively) were used for data analysis.

Data analyses

All data were collected on standardised forms and statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 20.0.0.1, IBM Corporation).

Continuous variables were displayed with an average (mean) and standard deviation (SD) or, in case of a non-normal distribution, as median and range. The normality was assessed by visual interpretation of histograms. Categorical variables were displayed as frequency (n) and percentage (%).

Differences between categorical variables in participant demographics were calculated by using chi-squared tests. Differences between continuous variables were calculated by using the unpaired T-test (with Welch correction if applicable) and, if data were not sampled from a Gaussian distribution, a non-parametric test was performed.

The relation between participants' characteristics, treatment preferences and indicated costs was determined by using Spearman's rank correlation coefficient (age), chi-squared (χ^2) (gender, ethnicity, marital status) and one-way analysis of variance (ANOVA) (income, education level) at univariate level. The Holm-Bonferroni method was used to counteract the problem of multiple comparisons. We constructed multivariate linear regression models to examine whether differences in treatment preferences between groups were related to the differences in demographic characteristics that were observed (variables with a $p < 0.15$ at univariate level). All statistical tests were two tailed. Differences were considered statistically significant at $p < 0.05$)

RESULTS

Participants' characteristics

Table 1 presents the characteristics of cancer patients, non-cancer patients and healthcare professionals. Cancer patients were significantly older in comparison with non-cancer patients and healthcare professionals (mean age 61 years; SD 14.5 years, 51 years; SD 17.5 years, and 41 year; SD 11 respectively, $p < 0.001$). While education level and gross income differed between healthcare professionals and the two patient groups, there was no difference between cancer and non-cancer patients.

Table 1. *Baseline characteristics of participants allocated by group*

Characteristics*	Patients with cancer (n = 139)	Patients without cancer (n = 82)	Healthcare professionals (n = 161)	p-value‡
Age years (SD)	61 (14.5)	51 (17.4)	41 (11)	<0.001**
< 65 years	70 (50)	64 (78)		
≥ 65 years	69 (50)	18 (22)		
Gender				
Male	59 (42)	37 (45)	59 (37)	0.38††
Education level†				
Low	36 (26)	20 (24)	-	
Mid	72 (53)	43 (53)	7 (4)	
High	29 (21)	19 (23)	152 (96)	<0.001
Marital status				
Living alone (Single, separated, widow)	32 (24)	24 (30)	26 (70)	0.08††
Gross income				
<€25,000	42 (32)	34 (43)	7 (4)	
€25,000-€50,000	56 (43)	32 (40)	39 (25)	
>50,000	32 (25)	14 (17)	113 (71)	<0.001**
Origin				
Dutch	132 (95)	77 (94)	154 (96)	0.56††
Preferred role in treatment decision				
Only I decide	6 (4)	3 (4)	8 (5)	<0.001††
Especially I decide	16 (12)	15 (18)	61 (37)	
Doctor and I decide equally	79 (58)	56 (68)	74 (46)	
Especially the doctor decides	32 (23)	7 (9)	18(11)	
Only the doctor decides	5(4)	1 (1)	0	
Cancer type				
Breast	36 (26)			
Colorectal	24 (17)			
Haematological malignancies	19 (14)			
Gynaecological	13 (9)			
Melanoma#	9 (7)			
Sarcoma#	6 (4)			
Head & Neck#	6 (4)			
Others (not specified)	26 (19)			

Values are numbers (percentages) unless stated otherwise. *For some variables a small proportion of data was missing for a maximum of 5 participants. †Highest qualification: high = university (of applied science); low = no education. ‡Between three groups. **Kruskall-Wallis test. ††Chi-square test. #All from Radboudumc.

Fifty-eight percent of cancer patients (78/134) were treated with palliative intent. Of these patients, 30% (41/134) were diagnosed with cancer less than three months ago and 87/139 patients (63%) had known metastatic disease. The most common cancers in the MST were breast (33%), colorectal (20%), and haematological malignancies (22%). Because the Radboudumc is a tertiary care centre, a higher percentage of rare tumours (sarcomas, head and neck cancers) was observed (*table 1*). The majority of participants desired an active participation in decisions about cancer treatment (shared decision-making). Healthcare professionals (as surrogate patients) more often opted for the option 'Only I decide' or 'Especially I decide'.

Treatment preferences

According to the two hypothetical chemotherapy regimens, subjects were first asked if 'under any circumstances' they would accept a mild or intensive cancer treatment (*table 2a*). For both regimes, the level of rejection was similar for cancer patients and non-cancer patients. Healthcare professionals were significantly more willing to accept chemotherapy compared with cancer patients and non-cancer patients (p = 0.01), with none of the professionals rejecting the mild regimen and 4.3% rejecting the intensive regime. Fifteen participants (4.5%, only patients) were willing to undergo the intensive therapy but not the mild therapy.

Participants who were willing to undergo a mild or an intensive regimen were asked to indicate a minimal desired treatment benefit in terms of cure, life prolongation and relief of symptoms (*table 2b*). Overall, the mean threshold for accepting a toxic regimen was higher or equivalent to that of the mild regimen. About 50% of all patients and 41.6% of the healthcare professionals desired the

Table 2a. *Respondents refusing mild and/or intensive treatment regimen*

Regime	Patients with cancer (1) n = 139	Patients without cancer (2) n = 82	Healthcare professional (3) n = 161	Pair wise comparisons¥		
				1 - 2	1 – 3	2 – 3
Mild n (%)	6 (4.3)	9 (11.0)	0 (0.0)	0.07	<0.01	<0.01
Intensive n (%)	24 (17.3)	16 (19.5)	7 (4.3)	0.68	<0.01	<0.01

Values are numbers (percentages) unless stated otherwise. ¥Chi-square test, Bonferroni-Holm correction for multiple comparisons.

Table 2b. *Minimal benefit to make a hypothetical chemotherapy treatment acceptable – a comparison between (1) patients with cancer, (2) patients without cancer and (3) healthcare professionals*

Regimen		Patients with cancer (1)	Patients without cancer (2)	Healthcare professional (3)		Pair-wise comparisons					
						Group 1 vs. Group 2		Group 1 vs. Group 3		Group 2 vs. Group 3	
Mild	**n**	133	73	161		**B* [95% CI]**	**p value**	**B* [95% CI]**	**p value**	**B* [95% CI]**	**p value**
	Probability of cure (%) mean (SD)	57 (29)	54 (24)	32 (22)	**Unadjusted**	-3 [-10, 4]	0.41	-24 [-30, -19]	<0.01	-21 [-28, -14]	<0.01
					Adjusted†	2 [- 6, 9]	0.66	-7 [-15, 2]	0.13	-18 [-26, -12]	<0.01
	Life prolongation (mo) median (range)	24 (0-60)	24 (1-60)	6 (0-60)	**Unadjusted**	-4 [-10, 2]	0.18	-16 [-21, -11]	<0.01	-12 [-18, -6]	<0.01
					Adjusted†	-1 [-7, 5]	0.77	-2 [-9, 5]	0.52	-1 [-8, 6]	0.69
	Symptom relief (%) mean (SD)	49 (29)	51 (26)	39 (21)	**Unadjusted**	2 [-5, 9]	0.55	-9 [-15, -4]	<0.01	-12 [-19, -5]	<0.01
					Adjusted†	6 [-2, 13]	0.13	5 [-4, 15]	0.26	-1 [-9, 8]	0.86
Intensive	**n**	115	66	154							
	Probability of cure (%) mean (SD)	56 (26)	58 (23)	44 (24)	**Unadjusted**	2 [-6, 10]	0.60	-13 [-19, -7]	<0.01	-15 [-22, -8]	<0.01
					Adjusted†	4 [-4, 11]	0.37	1 [-8, 9]	0.89	-3 [-12, 6]	0.53
	Life prolongation (mo) median (range)	24 (0-60)	24 (1-60)	12 (1-60)	**Unadjusted**	2 [-4, 8]	0.56	-10 [-15, -5]	<0.01	-12 [-18, -6]	<0.001
					Adjusted†	3 [-3, 10]	0.33	-2 [-9, 6]	0.71	-5 [-12, 3]	0.23
	Symptom relief (%) mean (SD)	50 (26)	58 (20)	54 (19)	**Unadjusted**	9 [2, 15]	0.01	4 [-1, 9]	0.15	-5 [-11, 2]	0.16
					Adjusted†	9 [3, 16]	<0.01	13 [5, 21]	<0.01	-3 [-10, 3]	0.30

Unadjusted and adjusted for education level; n = number; SD = standard deviation; CI = confidence interval; mo = months.
*B represents the differences in percentage or months between groups; †All adjustments were corrected for age and gender, and depending on the univariate analysis for potential confounders like education level. Significance level at 0.05.

same level of cure from both regimens. Remarkably, 9.4% of all patients indicated to want a higher benefit from the mild treatment. As presented by the unadjusted analyses, healthcare professionals demanded significantly less benefits from both therapies compared with cancer and non-cancer patients. No difference was found between cancer and non-cancer patients. Sub-analyses between oncology-oriented healthcare professionals (concerning both physicians and nurses, n = 51) and non-oncology healthcare professionals (remaining healthcare professionals, n = 108) showed no significant differences in willingness to undergo chemotherapy or indicated treatment benefit for both regimens.

To examine whether differences in preferences between groups are related to the differences in the demographic characteristics that were found, we adjusted for possible confounders. At an univariate level, the variables age, education level and gross income showed associations (data not shown). The variable gross household income was not put in the multivariate model, because of its collinearity with the education level. At multivariate level only the factor education level was an important explanatory determinant; adjusted for education, the observed difference between healthcare professionals and patients was no longer significant. Highly educated subjects accepted chemotherapy for significantly less benefit (mostly $p < 0.001$) compared with low-educated participants (*table 2b*). Although the average age between the three groups is different, there was no relation between age and indicated treatment benefits at the multivariate level.

Table 3 presents the relationships between baseline characteristics and treatment preferences in each group separately. In these models, treatment benefit is expressed by the desired cure rate. In patients with cancer, education and gender were associated with the desired treatment benefit. A higher education level was associated with lower treatment benefits for both cancer patients and non-cancer patients (in case of a heavy treatment regimen). With regard to chance of cure, female cancer patients were significantly ($p < 0.05$ in both regimens) more reluctant to undergo a mild ($p < 0.01$) or intensive regimen ($p = 0.02$) compared with men. However, in the group of healthcare professionals, men were more reluctant compared with their female colleagues to accept an intensive regimen ($p = 0.04$). Among cancer patients no correlation was found between age and desired cure rate. For healthcare professionals, there was a positive correlation between age and desired cure rate in the mild regimen ($p < 0.001$). In the intensive treatment regimen the p value was 0.12.

Cost valuation

Participants were presented a hypothetical situation in which they had cancer and were offered cancer treatment with a three-month survival benefit. They were asked to rate the maximum acceptable costs of this treatment. This was done for two hypothetical situations: one with a good performance state (scenario A) and one with a poor performance state (scenario B). *Figure 1* shows the results per survey group. Cancer patients accepted higher costs in both scenarios compared with healthcare professionals (good performance state $p = 0.018$; poor performance state $p = 0.012$). Between cancer patients and non-cancer patients there was no difference in valuation. A remarkable number of cancer patients (n = 27; 21.6%), non-cancer patients (n = 14; 17.9%) and healthcare professionals (n = 14; 8.9%) found a cost of more than €50,000 per month acceptable.

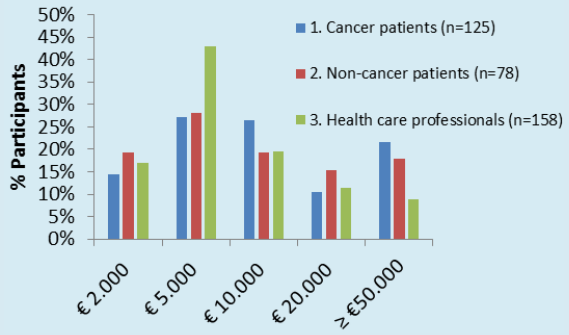
In all groups, the maximum acceptable costs of a cancer treatment for good performance state were significantly ($p < 0.001$) higher than for poor performance state, despite a comparable hypothetical survival gain in both scenarios. In contrast, about 5.3% (19/357) indicated a higher amount for a hypothetical new treatment acceptable in a patient in a poor performance state. For 60.5 (216/357) of participants,

Table 3. *Multivariate regression models of each group separately – both regimens with cure rate (%) as dependent factor*

Variables*	Mild regimen			Intensive regimen		
	Patients with cancer	Patients without cancer	Healthcare professionals	Patients with cancer	Patients without cancer	Healthcare professionals
Age	0.13	-	<0.001	-	-	0.12
Gender	<0.01	-	0.65	0.02	-	0.051
Marital status	-	-	-	-	-	-
Education level† Low High	 0.54 <0.01	-	-	 0.29 <0.01	 0.98 <0.01	-
Location*	-	-	-	-	<0.01	0.03

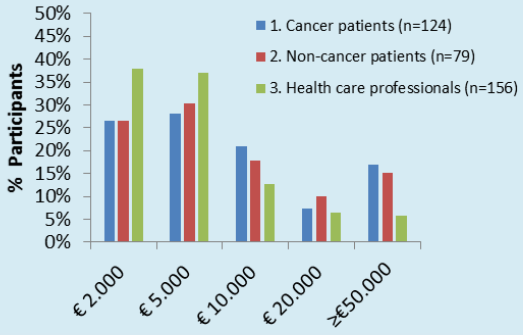
*Only variables with $p < 0.15$ at univariate level were entered into the multivariate regression models. †All healthcare professionals were high-educated. Significance level at 0.05.

Figure 1A. *Percentage distribution of the maximal acceptable costs per month for a new cancer treatment – with a benefit of three months life expectancy – for a patient in a good performance state*



p value for comparison between cancer and non-cancer patients: p = 0.55; p value between cancer patients and healthcare professionals p = 0.018; p value between non-cancer patients and healthcare professionals p = 0.22).

Figure 1B. *Percentage distribution of the maximal acceptable costs per month for a new cancer treatment -with a benefit of three months life expectancy -for a patient in a poor performance state*



p value for comparison between cancer and non-cancer patients: p = 0.93; p value between cancer patients and healthcare professionals p = 0.012; p value between non-cancer patients and healthcare professionals p = 0.10.

performance status had no influence on the maximum acceptable costs.

Again education level was of influence (the less educated accepted higher costs). No relations were found for age, gender and marital status.

DISCUSSION

We studied the willingness to accept chemotherapy and the attitudes towards of costs of cancer treatment in the Netherlands.

The main conclusions of our study are: (1) almost all patients accept chemotherapy, although the majority indicate unrealistic goals, (2) education level has a significant influence on preferences, while age only gave different views when tested univariately, and lastly, (3) regarding costs in cancer care, many cancer and non-cancer patients opted for higher cost options, thereby indicating that cancer costs should not be a topic of discussion according to patients.

Treatment preferences

The results of this study show a significant difference between patients and healthcare professionals. While minimal benefits did not differ between cancer patients and non-cancer patients, with respect to chance of cure, life prolongation and symptom relief, healthcare professionals were likely to accept chemotherapy for lower thresholds. Education level was the most important explanatory variable. Remarkably, the differences between patients and healthcare professionals disappeared when correction for education level was applied.

Despite a wide variety in desired benefit, the average desired benefit of both cancer and non-cancer patients accepting chemotherapy was high and beyond what is realistically achievable in most settings. This finding is contrary to the observed thresholds by Slevin et al.[5] However, two smaller but methodologically comparable studies by Bremnes[6] and Extermann[7] reported findings comparable to our study.

Given the indicated desired benefit, patients have too high expectations of chemotherapy. These unrealistic expectations are consistent with other studies demonstrating discordance between unrealistic expectations of patients and physicians' beliefs about treatment.[21,22] While high expectations of non-cancer patients could be explained by lack of familiarity with the treatment effect expected, all cancer patients in this study received chemotherapy with generally presumed less benefit compared with their indicated preferences in the given hypothetical situation. There are several explanations for these unrealistic expectations. A Dutch cancer-specific ethnographic study described that collusion between the cancer patient and physician (with explicit focusing on chemotherapy effects) may facilitate unrealistic optimism and unjustified hope.[23] 'Not giving up' is an attitude for physician and patient to reinforce considerations about chemotherapy.[24] Other factors include inability of physicians to communicate adequately about expected prognosis and using complex terminology, which is sometimes too difficult for patients to understand.[23,25]

Because the majority of participants indicated to prefer 'shared decision-making', the discrepancy in treatment preferences between patients and healthcare professionals

emphasise the importance of carefully discussing preferences and expectations before starting treatment.
Level of education appeared the most important extensive explanatory variable. An explanation for this finding could be that higher educated people have more knowledge about chemotherapy and therefore assess the risk/benefit ratio differently. Surprisingly, age did not appear to be of influence in the two patient groups. In contrast to previous studies, there was no difference in desired benefit between younger and senior patients (70 years and older).[10,26] As a result of the growing participation of the elderly in education with a better financial, health and care situation, older patients are more self-conscious and therefore perhaps more willing to undergo treatment.[27] As a consequence of this emancipation, age no longer seems to be a limiting factor.

Attitudes towards cancer costs

Recently, the costs of cancer care generated widespread headlines, and the Dutch Cancer Society wrote a report on accessibility of cancer drugs.[27] However, patients' preferences concerning costs of cancer treatment are relatively unknown. The annual Dutch costs of new anticancer agents are approximately €60,000 to 80,000 per patient. Most of these new agents do not cure, but only prolong life. Attitudes towards cancer costs varied between the three groups, with healthcare professionals accepting significantly lower maximum cost options in comparison with cancer patients. As expected, participants accepted higher costs for a patient with a good performance state. Many patients and non-cancer patients opted for the highest possible answer option '€50,000 or more per month', thereby indicating that cancer costs should not be a topic of discussion. Because costs of cancer care are directly covered by healthcare insurance in the Netherlands, most patients are unaware of the actual costs of their treatment and do not discuss treatment costs with their physician. This unawareness makes it hard to realise the personal economic burden of treatment costs. Although in this study participants were not directly asked on their view on the treatment cost debate, the questions about cost gave rise to emotional feedback, in which most patients emphasised that treatment costs should not influence the treatment and not be discussed directly between doctor and patient. Focusing on healthcare professionals, most professionals opted for low cost options (€2000 to €5000 per month). However, a small percentage indicated the highest possible amount. This finding emphasises a mismatch between one of the CanMEDS[1] competencies: 'The responsible use of healthcare recourses' and the individual physician who wants the best for his patient, regardless the costs. To gain more insight into attitudes towards cancer costs, new methodologies need to be developed, so that study results can be better compared and be uniform.[28] Physicians and policy makers will thus gain more insight into the value of health.
Lower educated participants with lower incomes indicated significantly higher values for treatment costs. This finding is contrary to several willingness to pay studies where income was related to the willingness to pay.[16,29,30] A possible explanation for this finding lies in the extension of the earlier mentioned relation between education level and desired treatment benefits. Higher educated participants, generally having higher incomes, may be more aware that an increasing amount of the gross domestic product is spent on healthcare and that this continuing increase is not durable in the long run.

Strengths and weaknesses of the present study

The strength of the present study includes the unique concept of analysing treatment preferences and attitudes towards societal cost in the Netherlands. By including participants in different regions and two different practice settings – an academic centre (Radboudumc) and a general hospital (MST) - we have probably created a representative Dutch patient population.
However, there are several limitations to be noted. First, because all participating cancer patients received chemotherapy and therefore already discussed treatment options and preferences with their physician, it is possible that they have a more positive view regarding therapy compared with cancer patients not scheduled for chemotherapy. Besides, because this study was carried out in a hypothetical situation, cancer patient preferences may have been influenced by the effect of reconciliation with the treatment decisions they have made before.[31]
A second important methodological limitation is related to the use of a questionnaire. Despite intensive testing and revision of the questionnaire, a small number of participants (less than 10%) desired conflicting treatment outcomes by indicating higher treatment benefits of a mild regimen, compared with an intensive regimen, suggesting they did not interpret the questions correctly. In addition to the present study, the next step would be to assess preferences of cancer patients and physicians by investigating underlying social-economic factors and using other strategies such as discrete choice and trade-off experiments. Combining these experiments with personal interviews would be an important addition to understand these, sometimes remarkable, outcomes. Application of willingness to pay strategies to analyse costs remains difficult, especially in Western Europe, where the healthcare system is organised differently compared with other parts of the world. Within this field, patients'

1 CanMEDS is an educational framework identifying and describing seven roles that lead to optimal health and healthcare outcomes: medical expert (central role), communicator, collaborator, manager, health advocate, scholar and professional.

perspectives regarding cancer costs are poorly studied.[25] Simplified and validated methods are needed to better assess attitudes towards cancer costs.

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ORIGINAL ARTICLE

Value of ^{18}F-FDG PET/CT in diagnosing chronic Q fever in patients with central vascular disease

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ABSTRACT

Background: The aim of this study is to describe the value of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in diagnosing chronic Q fever in patients with central vascular disease and the added value of ^{18}F-FDG PET/CT in the diagnostic combination strategy as described in the Dutch consensus guideline for diagnosing chronic Q fever.
Methods: ^{18}F-FDG PET/CT was performed in patients with an abdominal aortic aneurysm or aorto-iliac reconstruction and chronic Q fever, diagnosed by serology and positive PCR for *Coxiella burnetii* DNA in blood and/or tissue (PCR-positive study group). Patients with an abdominal aortic aneurysm or aorto-iliac reconstruction without clinical and serological findings indicating Q fever infection served as a control group. Patients with a serological profile of chronic Q fever and a negative PCR in blood were included in additional analyses (PCR-negative study group).
Results: Thirteen patients were evaluated in the PCR-positive study group and 22 patients in the control group. ^{18}F-FDG PET/CT indicated vascular infection in 6/13 patients in the PCR-positive study group and 2/22 patients in the control group. ^{18}F-FDG PET/CT demonstrated a sensitivity of 46% (95% CI: 23-71%), specificity of 91% (95% CI: 71-99%), positive predictive value of 75% (95% CI:41-93%) and negative predictive value of 74% (95% CI: 55-87%). In the PCR-negative study group, ^{18}F-FDG PET/CT was positive in 10/20 patients (50%).
Conclusion: The combination of ^{18}F-FDG PET/CT, as an imaging tool for identifying a focus of infection, and Q fever serology is a valid diagnostic strategy for diagnosing chronic Q fever in patients with central vascular disease.

KEYWORDS

Aneurysm, vascular graft, chronic Q fever, ^{18}F-FDGPET/CT, sensitivity, specificity

INTRODUCTION

Q fever is a zoonotic infection caused by *Coxiella burnetii*, an intracellular and Gram-negative bacterium. *C. burnetii* is globally present and the reservoir is found in various animals, such as goats, cattle, sheep and household pets. Humans can be infected by inhalation of contaminated aerosols.[1] Although often underdiagnosed, Q fever should be considered a public health problem in many countries such as France, Australia, United Kingdom, Italy, Spain, Germany, Israel, Greece and Canada. Q fever often goes unrecognised due to poor surveillance of the disease and the usually asymptomatic infection.[1,2] Two clinical forms of Q fever are described: acute Q fever and chronic Q fever. While primary *C. burnetii* infection is asymptomatic in 60% of all infected persons, the other 40% manifest with a self-limiting flu-like illness known as acute Q fever, which can be complicated by pneumonia or hepatitis.[1]

Chronic Q fever can develop months to years after primary infection. Patients with a history of cardiac valvulopathy or valvular surgery, an aneurysm or a central vascular graft (central vascular disease), non-haematological malignancy, pregnancy, renal insufficiency or older age are at risk of developing chronic Q fever.[3,4] Generally, 1-5% of all patients infected with *Coxiella burnetii* will develop chronic Q fever.[4,5]

Recently, we reported a study in which a large population of patients with central vascular disease were screened in a Q fever epidemic area in North-East Brabant, the Netherlands. A total of 16.8% of patients showed evidence of Q fever infection, of which 30.8% fulfilled the criteria of a chronic Q fever infection (in the context of central vascular disease, these infections could be considered what is referred to in the French literature as 'vascular' chronic Q fever).[6] These figures suggest that the rate of development to chronic Q fever among patients with central vascular disease is high. Chronic Q fever in patients with central vascular disease often manifests as a mycotic aneurysm or an infected vascular graft. These infections can be accompanied by life-threatening complications such as a ruptured aneurysm, aorta-enteric fistula, aorta-caval fistula and spondylodiscitis. Mortality rates of 13.3-40% in the absence of antibiotic therapy and surgical intervention have been reported.[7-10]

Diagnosing chronic Q fever is still challenging. The Dutch Q Fever Consensus Group published a diagnostic guideline based on the available literature and clinical experience, in which the probability of a patient having chronic Q fever is defined using serology, polymerase chain reaction (PCR) results in blood/tissue, clinical parameters, pathology and imaging studies, such as ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). The guideline categorises chronic Q fever patients as having proven, probable or possible disease.[11] Thus far, no real gold standard for the diagnosis of chronic Q fever is at hand. According to the Dutch consensus guideline, proven chronic Q fever is diagnosed if PCR for *C. burnetii* DNA is positive in blood or tissue, in the absence of acute Q fever infection, or in case of a patient with central vascular disease and a serological profile of chronic Q fever (IgG phase I titre ≥ 1:1024) and if large vessel or prosthetic infection is suggested by imaging (^{18}F-FDG PET/CT, CT, MRI or cardiac ultrasound). Probable chronic Q fever in patients with central vascular disease is diagnosed in case of a serological profile of chronic Q fever without a positive PCR or signs of infection by imaging.[11] Analysis of patients in the National Chronic Q Fever Database showed positive PCRs in the blood of only 44% of the patients with chronic Q fever.[12]

A recent study into the diagnostic performance of serology using the 1:1024 cut-off titre for IgG phase I revealed high sensitivity but low specificity for diagnosing proven chronic Q fever.[13,14] PCR for *C. burnetii* DNA in blood samples has a sensitivity of 50-70%, but a specificity of 100%.[1,13,14] The combination of outcomes of serology and PCR tests in blood is considered to provide the best reliable diagnostic criteria for chronic Q fever. ^{18}F-FDG PET/CT is included in the Dutch consensus guideline based on reports describing it as a promising tool for diagnosing infected aortic grafts and/or mycotic aneurysms. In patients with these conditions, ^{18}F-FDG PET/CT demonstrated a good diagnostic performance with a sensitivity of 91-93% and a specificity of 70-95%.[15-22] Additionally, ^{18}F-FDG PET/CT is a proven technique used in the work-up of patients with fever of unknown origin.[23] In the Dutch guideline for chronic Q fever, ^{18}F-FDG PET/CT is one of the imaging modalities proposed to identify a focus for infection. However, the value of ^{18}F-FDG PET/CT in this selected group of chronic Q fever patients is not yet well established. In 2013, Barten et al. reported an article in which ^{18}F-FDG PET/CT showed a focus of infection in 10 out of 13 patients with proven chronic Q fever (Q fever endocarditis and 'vascular' chronic Q fever), concluding that ^{18}F-FDG PET/CT is a helpful imaging technique for localising the infection site of chronic Q fever.[24] Furthermore, in the literature, two case reports describing the use of ^{18}F-FDG PET/CT in diagnosing an infected vascular graft in patients with chronic Q fever were published, both advising to use ^{18}F-FDG PET/CT in these patients.[25,26]

The aim of this study is to describe the single value of ^{18}F-FDG PET/CT in diagnosing chronic Q fever in patients with central vascular disease and evaluating the added value of ^{18}F-FDG PET/CT in the combination strategy in the Dutch consensus guideline. Therefore, we addressed the question how often ^{18}F-FDG PET/CT detects a vascular focus in patients with central vascular disease and proven chronic Q fever.

MATERIAL AND METHODS

Patients

From November 2009 to May 2012, all chronic Q fever patients with an aneurysm of the central arteries or a central vascular graft (abdominal aortic aneurysm (aorta ≥ 30 mm), aneurysm of the common iliac artery (> 12 mm) or aorto-iliac reconstruction, such as an endovascular aneurysm repair or open aorto-iliac reconstruction) and an IgG phase I titre ≥ 1:1024 were included in a multidisciplinary treatment program in the Jeroen Bosch Hospital in 's-Hertogenbosch and Bernhoven Hospital in Uden, the Netherlands. Within this program, ^{18}F-FDG PET/CT and transthoracic cardiac ultrasound were performed

to identify a focus for infection. Patients were partly retrospectively included and partly prospectively.

Patients were included in the PCR-positive study group if diagnosed with an IgG phase I titre ≥ 1:1024 and a positive PCR in blood or tissue; this combination of diagnostic criteria is considered the gold standard for proven chronic Q fever according to the Dutch consensus guideline. The PCR-negative study group included patients with an aneurysm of the central arteries or a central vascular graft and an IgG phase I titre ≥ 1:1024 but a negative PCR for *C. burnetii* DNA in blood and/or tissue. In these two patient groups, ^{18}F-FDG PET/CT was performed before starting any antibiotic treatment.

The control group consisted of patients with an aneurysm or a central vascular reconstruction and a negative serological profile for Q fever, in whom ^{18}F-FDG PET/CT was performed to evaluate an illness other than an infected aneurysm or vascular graft, with normal white blood cell (WBC) count and C-reactive protein (CRP) level.

Microbiological procedures

Sera were tested for *C. burnetii* antibodies using immunofluorescence assay (IFA, Focus Diagnostics, Inc., Cypress, CA, USA), assessing the presence of IgM and IgG antibodies to phase I and II antigens. If the IgG phase I titre was ≥ 1:512, sera were also tested by PCR for the presence of *C. burnetii* DNA. The NucliSensEasyMAG extraction system (bioMerieux, Boxtel, the Netherlands) was used for extraction of DNA from serum and/or tissue. PCR was performed as previously described.[27]

^{18}F-FDG PET/CT

All ^{18}F-FDG PET/CT scans were performed at the Department of Nuclear Medicine of the Jeroen Bosch Hospital, which is accredited by European Association of Nuclear Medicine Research Ltd. ^{18}F-FDG PET/CT was performed according to the European Association of Nuclear Medicine procedure guidelines.[28] Patients fasted for at least six hours before injection of ^{18}F-FDG. A dose of 4.5 MBq per kg was injected 60 min before the start of the scan. Scans were performed on a Biographm CT or Biograph 16 scanner (Siemens Medical Systems, Knoxville, TN, USA) scanning three minutes per bed position from the base of the skull to the middle of the femora. Covering the same area, low-dose CT was performed for attenuation correction. Data were reconstructed in three dimensions. PET, CT and fused images were reviewed using Syngovia software (Siemens). ^{18}F-FDG PET/CT scans were interpreted independently by two experienced nuclear physicians, aware of the suspicion of chronic Q fever. Scans were analysed using a visual grading scale in combination with the pattern of ^{18}F-FDG uptake as described in *table 1*.[9,18] In case of disagreement, a third reader was consulted and a final conclusion was made after a consensus meeting.

Infection parameters

WBC counts and CRP levels were retrieved from the hospital information system and compared for patients with a positive or negative ^{18}F-FDG PET/CT in the PCR-positive and PCR-negative Q fever study groups.

Table 1. *Interpretation of ^{18}F-FDG PET/CT combining a visual grading scale (A) and the pattern of uptake (B) adapted from Bruggink 2010 and Fukuchi 2005*

Interpretation of ^{18}F-FDG PET/CT
A. Visual grading scale
Grade 1: ^{18}F-FDG uptake similar to the background
Grade 2: Low ^{18}F-FDG uptake, comparable with inactive muscles
Grade 3: Moderate ^{18}F-FDG uptake, clearly visible and higher than inactive muscles
Grade 4: Strong ^{18}F-FDG uptake, comparable to physiological uptake in the bladder
B. Pattern
Homogeneous
Inhomogeneous
Conclusion (A+B)
High probability of infection or inflammation: (pathological uptake) Grade 3 or 4 and an inhomogeneous pattern
Sterile inflammation (no pathological uptake): Grade 3 or 4 and a homogeneous pattern
Normal: Grade 1 and 2
Interpretation ^{18}F-FDG PET/CT
1. Positive scan: focus for chronic Q fever in patients with central vascular disease: Conclusion 1
2. Negative scan: no focus for chronic Q fever in patients with central vascular disease: Conclusion 2 or 3

^{18}F-FDG PET/CT = 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography.

Clinical outcome

The clinical outcome in terms of cure was evaluated within the PCR-positive and the PCR-negative study groups between patients with a positive and negative ^{18}F-FDG PET/CT. Patients were considered cured if the IgG phase I titre reached < 1:1024. A favourable treatment response was defined as a fourfold or higher IgG phase I titre decrease with no or minimal clinical complaints.

Data analysis

Results of ^{18}F-FDG PET/CT in the PCR-positive patient group (gold standard) were compared with results in the control group to assess the diagnostic performance of ^{18}F-FDG PET/CT in finding a vascular focus for chronic Q fever. Within the PCR-negative group, ^{18}F-FDG PET/CT results were compared with those in the PCR-positive group. The diagnostic performance was expressed in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with Wilson 95% confidence intervals (CI). Mean WBC counts and CRP levels with standard deviations and p-values (Fisher's exact test and the single Chi-square test) were calculated using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

The study protocol is registered in Clinicaltrial.gov, a protocol registration system (registration number: NCT01450501 ID: 50-51800-98-013). The study was ethically approved by the local feasibility committees of the Jeroen Bosch Hospital and Bernhoven Hospital; approval of a regional Medical Research Ethics Committee was not necessary for this study as patients were treated according to the Dutch consensus guideline.

RESULTS

PCR-positive study group

Between November 2009 and May 2012, 13 patients were included in the PCR-positive study group and 22 in the control group. In three of the 13 patients in the PCR-positive study group, chronic Q fever infection was diagnosed by a positive PCR on tissue samples of the vascular wall, while ten patients were included due to positive PCR in blood. Transthoracic echocardiography was performed in all patients and none of them had signs of endocarditis. No abscesses or signs of spondylodiscitis were found in these patients with ^{18}F-FDG PET/CT. None of the patients included in this report were taking any medication such as prednisone, methotrexate, TNF-alpha and rituximab when ^{18}F-FDG PET/CT was performed. Fifty percent of the patients used a statin at the time of diagnosis; no difference was found between patients with or without statin use.

While reviewing the ^{18}F-FDG PET/CT scans, a third reader was consulted for two out of 35 scans (all in the positive-PCR study group); a final conclusion was made after a consensus meeting.

^{18}F-FDG PET/CT indicated pathological vascular uptake in six out of 13 (46%) patients in the PCR-positive study group, while no pathological uptake or a sterile inflammation was observed in three and four patients, respectively (as shown in *figure 1*). In the control group, ^{18}F-FDG PET/CT showed pathological vascular uptake in two out of 22 (9%) patients. One of the positive patients had undergone endovascular aneurysm repair in 2003, while the other one had received an aortic graft in 2006. Follow-up after 72 and 108 months (solely based on clinical follow-up, no second ^{18}F-FDG PET/CT was performed), respectively, revealed no signs of an infected graft (*table 2*). In the remaining 20 patients, no pathological uptake was observed in nine patients (one patient with a central graft and eight patients with an aneurysm), while eleven patients showed signs of a sterile inflammation (four patients with a central graft and seven patients with an aneurysm). ^{18}F-FDG PET/CT has a sensitivity of 46% (95% CI: 23-71%), specificity of 91% (95% CI: 71-99%), PPV of 75% (95% CI: 41-93%) and NPV of 74% (95% CI: 55-87%) for detecting chronic Q fever in patients with central vascular disease (*table 3*). Two of the three patients with a positive *C. burnetii* PCR of the vascular wall showed a positive ^{18}F-FDG PET/CT.

We checked for differences in uptake (especially a difference in homogeneous and heterogeneous uptake) between patients with an aneurysm or graft (*table 4*). No differences were found and therefore we decided it is valid to combine the two groups (p = 0.169). Additionally, the distribution in the pattern of uptake is distinctly different in the grade 1/2 and grade 3/4 group. In grade 3/4 a clear difference in distribution of pattern of uptake is seen between the PCR-positive group and the control group.

Table 5 shows the mean WBC count and CRP level in patients in the PCR-positive study group with a positive ^{18}F-FDG PET/CT compared with patients with a negative ^{18}F-FDG PET/CT. No significant differences were observed (p = 0.434 and p = 0.640, respectively).

PCR-negative study group

Twenty patients were evaluated in the PCR-negative study group. ^{18}F-FDG PET/CT showed pathological vascular uptake in ten out of 20 (50%) patients. In the remaining ten patients, no pathological uptake was observed in five cases, while ^{18}F-FDG PET/CT was indicative of a sterile inflammation in the other five patients. The percentage of positive ^{18}F-FDG PET/CT scans within the PCR-positive group did not differ from the number of positive ^{18}F-FDG PET/CT scans in the PCR-negative group (46% versus

Figure 1. *High probability of infection or inflammation (pathological uptake) in the wall of an aortic aneurysm (A) and sterile inflammation (no pathological uptake) of a Dacron aortic graft (B) with ^{18}F-FDG PET*

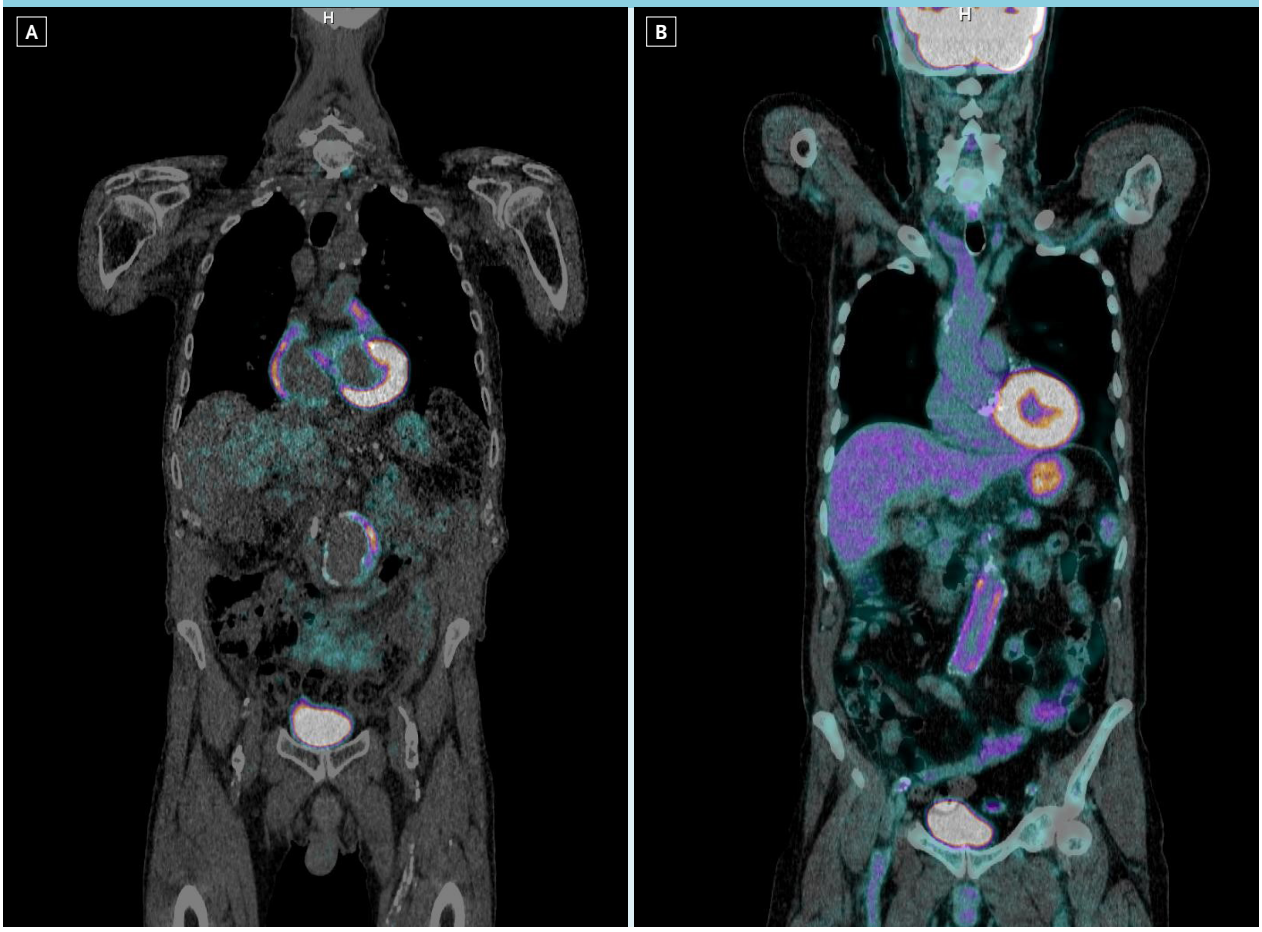

Table 2. *Results of ^{18}F-FDG PET/CT; number of patients with pathological uptake versus no pathological uptake on ^{18}F-FDG PET/CT in the PCR-positive study group and control group*

	PCR-positive study group	Control group	Total
Pathological uptake on ^{18}F-FDG PET/CT	6	2	8
No pathological uptake on ^{18}F-FDG PET/CT	7	20	27
Total	13	22	35

^{18}F-FDG PET/CT = 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography.

50%). Additionally, one patient without pathological uptake of ^{18}F-FDG on PET/CT within the PCR-negative group subsequently underwent surgery (after closure of the study) and the vascular wall tissue was found to be *C. burnetii* PCR positive. In the PCR-negative study group, infection parameters were low in patients with a positive ^{18}F-FDG PET/CT as well as in patients with a negative ^{18}F-FDG PET/CT without significant differences (see *table 5*).

DISCUSSION

Considering the high morbidity and mortality in patients with chronic Q fever and central vascular disease, diagnosing the disease is key to starting early treatment and preventing complications. In the Dutch consensus guideline for diagnosing chronic Q fever, ^{18}F-FDG PET/CT is listed as one of the imaging tools available to identify a focus of infection. Previous literature concluded

Table 3. *Diagnostic performance of ^{18}F-FDGPET/CT in diagnosing chronic Q fever in patients with central vascular disease*

Statistical measure	Performance	Range
Sensitivity	46%	19-63%
Specificity	91%	79-100%
PPV	78%	51-100%
NPV	77%	61-93%

NPV = negative predictive value; PPV = positive predictive value.

that ^{18}F-FDG PET/CT is a helpful imaging technique for localising the infection site caused by a chronic Q fever infection.[24] Furthermore, ^{18}F-FDG PET/CT is a valuable imaging tool to identify a vascular prosthesis infection with a sensitivity ranging from 91-93% and a specificity of 70-95%.[7,9,18] When scans are visually analysed, combining a grading scale with the pattern of ^{18}F-FDG uptake, the specificity significantly improved from 70 to 95% as shown in a study by Fukuchi et al.[9] This method was also applied in this study and a difference in distribution of pattern of uptake (homogeneous or heterogeneous) was seen between the PCR-positive group and control group implying that the pattern of uptake is of added value. However, a differentiation between inflammation and infection cannot be made with ^{18}F-FDG, as is mentioned in *table 1*. Although the specificity of 91% that we observed is in line with the results of Fukuchi et al., a much lower sensitivity was observed in our PCR-positive study group with proven chronic Q fever patients and central vascular disease.

The explanation for the observed low sensitivity is not clear. As a result of increased glycolytic activity, inflammatory cells (neutrophils and macrophages) as well as tumour cells show increased uptake of ^{18}F-FDG at sites of inflammation, infection and malignancy.[29] One report by Lepidi et al. described a histopathological quantitative analysis on infiltrating cells comparing the valve tissue of patients with Q fever endocarditis to non-Q fever-infected valve tissue.[30] It was demonstrated in this study that valve tissue damaged by chronic Q fever infection was localised in different parts of the valve and often concerned small and discrete regions.[29] If such discrete changes are also

Table 4. *Presenting the data on ^{18}F-FDG uptake divided into patients with an aneurysm and graft*

Graft (n = 32)	Grade 1 and 2		Grade 3 and 4	
	Homogeneous	Heterogeneous	Homogeneous	Heterogeneous
Q+ (PCR positive)	1	0	3	3
Q- (control group)	3	0	4	2
Q (PCR negative)	2	0	6	8
Aneurysm (n = 23)	**Grade 1 and 2**		**Grade 3 and 4**	
	Homogeneous	**Heterogeneous**	**Homogeneous**	**Heterogeneous**
Q+ (PCR positive)	1	0	2	3
Q- (control group)	7	1	4	1
Q (PCR negative)	1	1	1	1

Table 5. *Mean (± standard deviation) white blood cell count and C-reactive protein level in patients in the PCR-positive study group and in patients in the PCR-negative group comparing patients with a positive scan and a negative scan for chronic Q fever in patients with central vascular disease*

Infection parameter	Positive ^{18}F-FDG PET/CT	Negative ^{18}F-FDG PET/CT	p-value
PCR-positive study group (n = 13) White blood cell count	7.8 x 10^9/l ± 2.2	9.0 x 10^9/l ± 2.4	0.583
C-reactive protein level PCR-negative study group (n = 20)	14 mg/l ± 4	38 mg/l ± 49	0.396
White blood cell count	8.3 x 10^9/l ± 2.4	7.8 x 10^9/l ± 1.6	0.705
C-reactive protein level	1 mg/l ± 3	5 mg/l ± 7	0.359

^{18}F-FDG PET/CT = 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography.

present in chronic Q fever with a vascular focus, this could be an explanation for the low sensitivity of ^{18}F-FDG PET/CT in the PCR-positive study group. Further research, especially on histopathology of the vascular tissue, is needed to confirm this hypothesis. Recently, we published a report concerning the histopathology of the vascular wall in patients with chronic Q fever with a vascular focus in which we demonstrated a necrotising granulomatous infiltration response in only four out of seven patients. Unfortunately, the number of patients was too small to correlate with the results of the ^{18}F-FDG PET/CT.[31]

In the Dutch consensus guideline, proven chronic Q fever in patients with central vascular disease is diagnosed either by PCR positivity or through the combination of a serological profile matching chronic Q fever and proven large vessel or prosthetic infection by imaging studies such as ^{18}F-FDG PET/CT.[11] As the IgG phase I cut-off titre of ≥ 1:1024 has a sensitivity of 97.8% and a specificity of < 21.4% for diagnosing proven chronic Q fever, an imaging test with a high specificity would be beneficial for the diagnostic strategy presented in the Dutch consensus guideline.[11] Due to the high specificity of the ^{18}F-FDG PET/CT observed in this report (91%), we think it is acceptable to categorise patients with central vascular disease, an IgG phase I titre ≥ 1:1024 (high sensitivity) and a positive ^{18}F-FDG PET/CT (high specificity) as having proven chronic Q fever, as recommended in the Dutch consensus guideline. PCR-negative patients with central vascular disease, an IgG phase I titre ≥ 1:1024 and a negative ^{18}F-FDG PET/CT are classified as having probable chronic Q fever. Long-term antibiotic treatment and optional surgical intervention in patients with central vascular disease and proven chronic Q fever is advised.[32,33] Treatment of a patient with probable chronic Q fever and central vascular disease is more debatable and depends on the possible advantages and disadvantages of this treatment for the individual patient. In clinical practice, however, most patients with probable chronic Q fever in the Netherlands are treated with antimicrobial therapy in view of the risk of acute complications and mortality.[6,34]

In contrast to previous reports, in the wake of the 2007-2010 Dutch Q fever epidemic, a vascular focus of infection (57%) was more often found than an endocarditis focus (35%) among 215 patients with proven and probable chronic Q fever, while imaging studies revealed that the focus of infection may have been both heart valves and vascular structures in only 11 chronic Q fever patients. It is therefore not surprising that endocarditis was absent in our group of Dutch chronic Q fever patients with a vascular infection focus.[12]

After closure of the study, one patient with a serological profile of chronic Q fever (IgG phase I titre = 1:4096), a negative PCR in blood and negative ^{18}F-FDG PET/CT, underwent surgery and the vascular wall tissue was found to be positive for *C. burnetii* DNA by PCR. This emphasises the questionable value of both a negative ^{18}F-FDG PET/CT and negative PCR in the blood in patients with a known risk factor and a positive serological profile for chronic Q fever. The fact that a similar number of ^{18}F-FDG PET/CT positive results in the PCR-negative group (ten out of 20) was observed compared with the PCR-positive study group (six out of 13) also suggests that PCR in blood lacks sufficient sensitivity in patients with a known risk factor and a positive serological profile for chronic Q fever. The future could bring us more information concerning the diagnostic value of the different tests used in the Dutch consensus guideline. This might result in revision of this guideline, improving the healthcare for patients with chronic Q fever and central vascular disease, provide indications for an early start to treatment and prevent complications.

Limitations of this study are the low number of included patients and the fact that the reviewers of the scans were not blinded for outcome. Another limitation is the lack of a true gold standard for chronic Q fever with a vascular focus. PCR data on vascular tissue were absent in most patients as no surgical treatment or autopsy was performed in 10/13 patients in the PCR-positive group and 0/20 patients in the PCR-negative group.

CONCLUSION

The combination of ^{18}F-FDG PET/CT, as an imaging tool for identifying a focus of infection, and Q fever serology is a valid diagnostic strategy for diagnosing chronic Q fever in patients with central vascular disease.

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DISCLOSURES

There are no conflicts of interest.

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CASE REPORT

Good's syndrome: an uncommon cause of therapy-resistant diarrhoea

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ABSTRACT

Diarrhoea is a common symptom for which the aetiology will be straightforward in many cases. However, when a common aetiology is not found, the wide variety of other options can feel like finding a needle in a haystack. In this case report, we describe a patient who was referred to our centre with therapy-resistant, secretory diarrhoea, which was the presenting symptom of Good's syndrome, a rare form of adult-onset immunodeficiency associated with thymoma. The conclusions from this case report give direction for 'finding the needle' and contribute to a focused approach to patients who present with therapy-resistant diarrhoea.

KEYWORDS

Good's syndrome, secretory diarrhoea, thymoma

CASE REPORT

A 74-year-old Caucasian woman was referred to our centre because of therapy-resistant secretory diarrhoea for six weeks, resulting in severe weight loss of 15 kilograms (27% of her total body weight). Her medical history included oral lichen planus and atypical nodular lesions on her legs, diagnosed as keratoacanthoma. Four weeks after onset of diarrhoea, a colonoscopy was performed which revealed active colitis and nonspecific inflammation on pathological examination. On macroscopic examination during colonoscopy and microscopic examination the colitis was regarded as not specific for cytomegalovirus. Corticosteroids and mesalazine were started. However, after a few days she was admitted to the intensive care because of renal impairment and severe metabolic acidosis due to excessive gastrointestinal fluid and bicarbonate loss. Repeated blood and faecal cultures, including *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter* and *Clostridium*, remained negative. The patient was tested for HIV and found negative.

A paraneoplastic disease was suspected as the aetiology of the secretory diarrhoea. Octreotide was started to control fluid and electrolyte loss. Computed tomography (CT) scanning was performed in search of a neuroblastic or neuroendocrine tumour or thymoma. An anterior mediastinal mass was detected on chest X-ray and subsequent fluorodeoxyglucose (FDG) positron emission tomography (PET) with low-dose CT (FDG-PET/CT) scanning showed some uptake in this anterior mediastinal mass, without uptake in mediastinal lymph nodes or distant localisation. *Figure 1* shows the chest X-rays and an image of the CT scan with the anterior mediastinal mass. The findings were consistent with thymoma.

At that time the patient developed leukopenia and lymphocytopenia. The immunoglobulins were very low: IgA < 0.07 g/l (0.7-4.0 g/l) and IgM < 0.04 g/l (0.4-2.3 g/l). IgG was normal, but IgG subclass 4 was decreased (< 0.07 g/l (0.08-1.4 g/l)). The paraneoplastic antibody vasoactive intestinal polypeptide was negative.

What was known on this topic?

Good's syndrome is a paraneoplastic phenomenon in patients with thymoma. Patients have hypogammaglobulinaemia, a reduced B cell and CD4+ T cell count and present with recurrent infections and autoimmune manifestations. Diarrhoea is observed in 50% of patients

What does this case add?

Patients with Good's syndrome can present with therapy-resistant secretory diarrhoea. Clinicians should consider this syndrome in patients presenting with diarrhoea without known aetiology.

Table 1. *Summary of the WHO histological classification of thymomas*[1]

Type	Histological description
A	Type A thymoma is composed of bland spindle/oval epithelial tumour cells with few or no lymphocytes. The tumour cells can form a variety of histological structures
AB	Composed of a mixture of a lymphocyte-poor type A thymoma component and a more lymphocyte-rich type B-like component. Lymphocytes are more numerous than in the type A component, but may be less numerous than in B1 thymomas
B1	Resembles normal functional thymus with an appearance practically indistinguishable from that of normal thymic cortex with areas resembling thymic medulla
B2	Type B2 thymoma is composed of large, polygonal tumour cells that are arranged in a loose network and exhibit large vesicular nuclei with prominent large nucleoli, closely resembling the predominant epithelial cells of the normal thymic cortex. A background population of immature T cells is always present and usually outnumbers the neoplastic epithelial cells
B3	Type B3 thymoma is an organotypic thymic epithelial tumour predominantly composed of medium-sized round or polygonal cells with slight atypia. The epithelial cells are mixed with a minor component of intraepithelial lymphocytes
(C)	Heterogeneous group of thymic carcinomas (called type C thymomas in the previous WHO classification) that comprise malignant, usually invasive epithelial tumours with clear-cut atypia, largely absent organotypic features and a very diverse differentiation, resembling carcinomas outside the thymus

The combination of secretory diarrhoea, an anterior mediastinal mass and hypogammaglobulinaemia were suggestive for Good's syndrome.

Thymectomy via sternotomy was scheduled and performed uneventfully. Pathological examination of the resected specimen confirmed the suspected diagnosis: in this case type A thymoma of 13.8 cm in diameter with clear surgical margins according to the WHO classification of thymomas[1] (*table 1*). *Figure 2* shows a macrophoto of the thymoma with intact encapsulation. Type A thymoma is a medullary subtype composed of bland spindle cells and few lymphocytes. The tumour was encapsulated, both on macroscopic and microscopic examination. Therefore, the patient was classed as Masaoka stage I thymoma[2] (*table 2*). After surgery, her condition improved and the diarrhoea resolved. During follow-up, diarrhoea did not recur, neither did patient suffer from any infections.

DISCUSSION

Good's syndrome is a paraneoplastic phenomenon associated with thymoma, which was first described by Robert Good in 1954.[3] Thymoma is a rare epithelial

Figure 1. *A. Chest X-ray (PA) of our patient showing increased mediastinal volume. B. Lateral chest X-ray of our patient with obliteration of the retrosternal clear space. C. CT scan showing a large mass located in the anterior mediastinum, suspicious for thymoma*

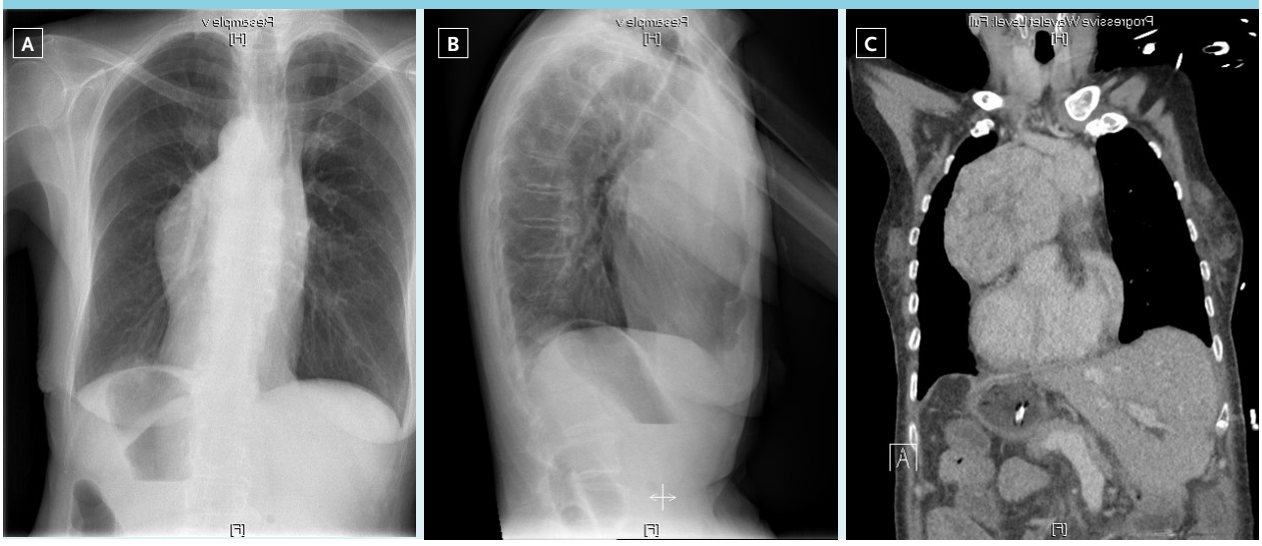
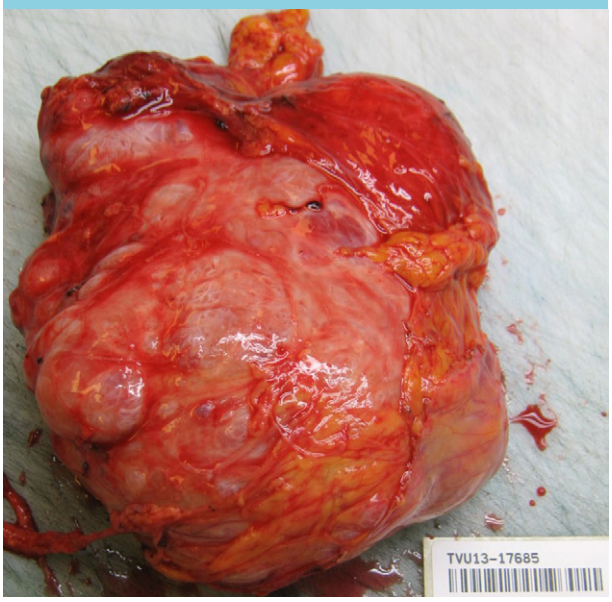


Table 2. *Masaoka staging of thymoma, modified since publication*[2]

Stage	Microscopic and macroscopic description
I	Macroscopically and microscopically encapsulated
II	Invasion beyond the capsule and into the nearby fatty tissue or the pleura. Sometimes divided into: IIa Microscopic transcapsular invasion IIb Macroscopic capsular invasion
III	Macroscopic invasion into the neighbouring tissues or organs of the lower neck or upper chest area, including the pericardium, lungs, or main vasculature
IVa	Widespread pleural and pericardial dissemination
IVb	Haematogenous or lymphatic dissemination; distant metastases

Figure 2. *Macroscopic image of the tumour that was surgically removed from our patient*



neoplasm originating from the thymus gland. This organ in the anterior mediastinum is present at birth and normally involutes at older age. Patients with thymoma may complain of symptoms secondary to the location of the anterior mass. These symptoms include hoarseness, dysphagia, dyspnoea, cough and chest pain. Histologically, thymomas are classified based on the shape of the epithelial cells. The prognosis for Masaoka stage I is excellent.[2]

Thymoma is best known for its association with myasthenia gravis, but it is also associated with other paraneoplastic syndromes. Patients with Good's syndrome typically have hypogammaglobulinaemia and a reduced B cell and CD4+ T cell count. The clinical presentation is usually determined by the underlying immunodeficiency. This affects both humoral and cellular components.[4]

The pathogenesis of Good's syndrome is unclear but the haematological deficiencies suggest an underlying bone marrow disorder. The majority of patients (83%) present with recurrent infections, followed by autoimmune manifestations (59%) such as oral lichen.[4,5] In almost 50% of patients, diarrhoea is the presenting symptom of Good's syndrome.[4-6] Thus far, the underlying mechanism of secretory diarrhoea associated with Good's syndrome is unclear. However, several mechanisms are postulated. Diarrhoea might be related to an infectious aetiology, as in some patients a pathogen is found such as *Salmonella*, cytomegalovirus, *Campylobacter* and *Giardia lamblia*, or bacterial overgrowth is detected.[7] In our patient, no infectious pathogen was found, neither in faecal nor blood cultures.

Another aetiology of diarrhoea associated with Good's syndrome that is proposed is described as an autoimmune enteropathy with watery diarrhoea and malabsorption, due to mucosal lesions and villous atrophy as autoantibodies against enterocytes can be found in some patients.[7,8] The mechanism of autoimmunity is not completely understood, but it might be associated with disordered thymic epithelial function.[8] In healthy individuals, the thymus is involved in the processing and maturation of T-lymphocytes that are released into the circulation upon maturation. Thymomas can disrupt this function.[8]

Furthermore, multi-organ involvement is also described in the literature.[8,9] Patients can present with chronic diarrhoea, skin eruptions and abnormal liver enzymes. Histopathological findings of bowel mucosa are similar to that seen with graft-versus-host disease.

Good's syndrome is treated by thymectomy, and infection prevention by giving gamma globulins and prophylactic antibiotics. Despite this treatment, the majority of patients succumb to the consequences of immunodeficiency and autoimmune diseases, with a ten-year survival of only 33%.[8]

In our patient, the diarrhoea almost immediately improved after surgery. This suggests an autoimmune pathogenesis

with disrupted thymic function. However, symptoms can persist or even arise years after thymectomy.[6]

Diarrhoea can be used as a follow-up marker for our patient or for patients who presented with this symptom. If the diarrhoea recurs, one should be aware that the tumour is back. This also applies to recurrent infections.

Finding the aetiology of therapy-resistant diarrhoea can be challenging when the most common causes are excluded and a patient remains therapy resistant. Imaging of the thorax in a patient with unexplained diarrhoea may lead to finding relatively rare paraneoplastic syndromes such as Good's syndrome.

DISCLOSURES

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CASE REPORT

Left atrial thrombus under dabigatran in a patient with nonvalvular atrial fibrillation

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ABSTRACT

Dabigatran is a new direct competitive inhibitor of thrombin and is equally effective and safe as warfarin in the prevention of thromboembolism in patients with nonvalvular atrial fibrillation. We present a case of a 60-year-old man with persistent nonvalvular atrial fibrillation who switched from acenocoumarol to dabigatran 110 mg twice daily. After five months the patient developed a large atrial thrombus, occlusion of the tibial arteries of the right foot, cerebellar infarction and multiple infarctions in kidneys and spleen. Blood test showed a dabigatran concentration of 35 ng/ml six hours after intake, correlating with a low trough concentration of 24-27 ng/mL and significantly increased thromboembolic risk. Other risk factors for thromboembolism were excluded. The present case indicates that in selected patients, there might be an indication for dose adjustments based on serum levels of dabigatran to ensure patient efficacy (thromboembolic events) and safety (bleeding).

KEYWORDS

Stroke prevention, atrial fibrillation, direct antithrombin agents, systemic embolism

INTRODUCTION

Atrial fibrillation (AF) is an important risk factor for thromboembolic events such as stroke and systemic thromboembolism. Oral vitamin K antagonists such as warfarin have been the treatment of choice in preventing thromboembolic events in patients with AF. However, frequent dose adjustment, slow onset of action, and monitoring of coagulation status, including multiple drug and food interactions, complicate routine use.

Therefore, several new direct oral anticoagulants (DOAC), including dabigatran etexilate, have been developed. Dabigatran etexilate is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive inhibitor of thrombin (factor IIa). Dabigatran specifically and reversibly binds and inactivates not only free but also fibrin-bound thrombin, leading to a reduction in fibrin clot formation and platelet aggregation. As this agent acts differently to warfarin, the bleeding time and INR will often be normal. Dabigatran has an absolute bioavailability of 6.5%, 80% of the given dose is excreted by the kidneys and its serum half-life is 12 to 17 hours.[1]

Dabigatran was first approved by the European Commission and the US Food and Drug Administration to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, a randomised trial comparing two doses of dabigatran (110 mg twice daily and 150 mg twice daily), given as a fixed dose without laboratory monitoring, with coumarin, showed similar or reduced rates for stroke or systemic embolism, without an increase in bleeding.[1] Further, dabigatran has been studied and approved for the treatment and prevention of recurrence of deep vein thrombosis and pulmonary embolism as well.

Based on the pharmacokinetics and pharmacodynamics of dabigatran, a fixed-dose treatment without the need for coagulation monitoring has been advised. However, significant variations in plasma levels between patients have been described with the occurrence of thromboembolic events and bleeding in patients with dabigatran pharmacotherapy.[2-4]

In this report we describe a patient with nonvalvular AF with the formation of a left atrial thrombus and severe thromboembolic events after treatment with dabigatran.

CASE REPORT

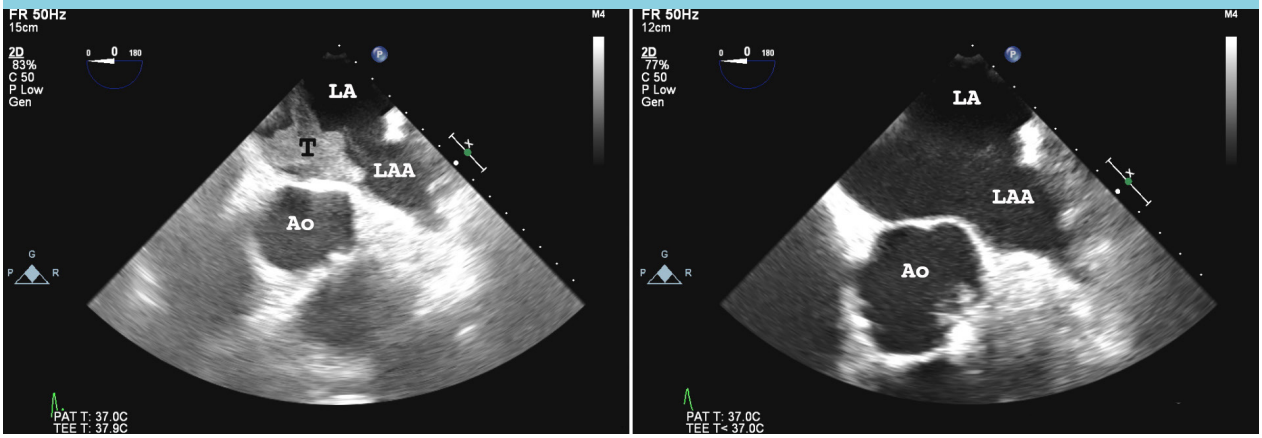
A 60-year-old Caucasian male, BMI 28 kg/m², was known with persistent AF. Besides an episode of ultrasound-proven diverticulitis two years ago, the patient had no relevant medical history. In 1995, at the age of 40 years, the patient suffered from peripheral embolism in his right hand and a transient ischaemic attack in the right cerebral hemisphere based on newly diagnosed AF. After this, he was treated with acenocoumarol with a target prothrombin international normalised ratio of 2.5 to 3.5 without suffering bleeding or embolic complications. During those years, the patient had several recurrences of AF, which were treated with direct current cardioversions. In 2010, the patient underwent pulmonary vein isolation; during this procedure, the left atrium was severely enlarged with fibrotic areas. After ablation, the AF recurred and persistent AF was accepted. Five months before presentation, on the patient's request, he switched from acenocoumarol to dabigatran 110 mg twice daily. The rationale behind this low dose of dabigatran was anticipating an increased risk for lower intestinal haemorrhage due to colonic diverticulosis and the fact that dabigatran 110 mg twice showed to be non-inferior to coumarin in the RE-LY trial.

At presentation, the patient complained of right calf pain and mild amnesia for four days. Physical examination showed a livid discoloration and cold right forefoot with a reduced posterior tibial pulse on the right side. No other abnormalities were found. The patient's medication was dabigatran 110 mg twice daily, verapamil 40 mg twice daily and omeprazole 40 mg daily. He was reportedly compliant with his medication and he had no history of trauma, surgery, immobilisation or smoking. Family history was negative for clotting disorders. At admission he had a dabigatran level of 35 ng/ml, assessed to verify compliance, measured six hours after the last reported dabigatran intake. The estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula was 49 ml/min/1.73 m² and one day after fluid infusion 65 ml/min/1.73 m². There were no other laboratory abnormalities and the dabigatran level was not measured before his current event. CT angiography of the legs showed acute thrombosis of the anterior tibial and posterior tibial artery. After intra-arterial thrombolysis, his symptoms improved slightly.

Transthoracic echocardiography showed a normal left ventricular function, an enlarged left atrium (63 ml/m²), but no cardiac source of embolism. However, subsequently, transoesophageal echocardiography demonstrated a large left atrial thrombus (*figure 1*, left panel). Magnetic resonance imaging of the cerebrum showed a small infarction of the posterior inferior cerebellar artery.

To exclude underlying malignancy, CT scans of the chest, abdomen and pelvis were performed, showing multiple small infarctions in the kidney and spleen. Risk factors for venous and arterial thrombosis were established, including protein S, protein C, antithrombin activity, factor VIII activity, lupus anticoagulant, anti-b2-glycoprotein antibodies, anti-cardiolipin antibodies, the platelet count, lipoprotein analysis, paroxysmal nocturnal haemoglobinuria analysis and DNA analysis for mutations in factor II and factor V. All were negative, only a dubiously positive lupus anticoagulant was noted, which we related to the presence of dabigatran in the sample. Due to the medical necessity of anticoagulation therapy, lupus anticoagulant presence could not be verified in a later state. The patient was hospitalised, dabigatran was ceased and we initiated treatment with enoxaparin 1 mg/kg twice daily and clopidogrel 75 mg once daily. Surgical removal of the left atrial thrombus was considered, but not performed. Except for a transient paresis of the left hand, no additional thromboembolic events occurred. The patient was discharged, after resumption of acenocoumarol (with INR range between 3.5-4.5) and continuation of clopidogrel. One month after presentation, a new transoesophageal

Figure 1. *Left: TEE image showing left atrial appendage (LAA), transverse view of the ascending aorta (Ao), and a large thrombus (T) at the anterior wall of the left atrium (LA). Right: 6 weeks later, corresponding TEE image, now showing complete resolution of the left atrial thrombus*



echocardiography was performed, now demonstrating complete resolution of the left atrial thrombus (*figure 1*, right panel). The patient was discharged, after resumption of acenocoumarol and continuation of clopidogrel. After follow-up of 12 months, no recurrent thromboembolic events occurred.

DISCUSSION

VKAs are effective for reducing the risk of thromboembolic stroke in AF patients.[5] However, frequent laboratory monitoring and dosage adjustments are required, due to a narrow therapeutic window and multiple interactions. Recent studies have demonstrated that dabigatran is at least equally effective.[6] Because of the claimed predictable pharmacokinetics, dabigatran was recommended at a fixed dose and does not require coagulation monitoring and/or laboratory test-guided dosage adjustments.[7]

Since the introduction of dabigatran, a few case reports have been published describing the occurrence of thromboembolic events in the setting of dabigatran pharmacotherapy. Sargento-Freitas et al. described a case of a 70-year-old female patient with an acute ischaemic stroke on dabigatran 110 mg twice daily. The dabigatran plasma peak concentration of confirmed therapy intake was 40.6 ng/ml. After dosage adjustment to dabigatran 150 mg twice daily, low peak concentrations persisted.[3] Sharma et al. report two cases of large left atrial thrombi and occurrence of thromboembolic events in patients with chronic AF compliant with recommended dabigatran therapy.[2]

Results on dabigatran plasma concentrations showed a high inter-individual variation in plasma levels of dabigatran. In a pre-specified analysis of RE-LY, plasma concentrations of dabigatran showed a fivefold variation, and were related to clinical outcomes of ischaemic stroke/systemic embolism and major bleeding.[1] As a result, the use of plasma concentrations for tailoring dabigatran dosing is the subject of on-going discussion.[8,9]

In our patient we measured a dabigatran value of 35 ng/ml at six hours after dosing. Assuming a dabigatran half-life of 12-17 hours, a dabigatran trough concentration of approximately 24-27 ng/ml can be expected. Based on the data of Reilly et al.[1] this would lead to a median hazard ratio for thrombotic risk of at least 1.5 (confidence interval 1.1-2.2). This illustrated that our patient had a significantly increased risk for ischaemic stroke and systemic embolism, for which increasing the dabigatran dose might be beneficial. Although the dabigatran plasma concentration was low, the impaired renal function and concomitant use of verapamil could have increased the dabigatran plasma concentration in our patient.[10] As a result, plasma dabigatran could have been even lower in case of normal renal function and absence of verapamil.

In conclusion, we describe a patient with several thromboembolic events under dabigatran 110 mg twice daily treatment with a low dabigatran plasma concentration. This case report shows that in selected patients there might be an indication for dose adjustments based on serum levels of dabigatran to ensure patient efficacy (thromboembolic events) and safety (bleeding). We suggest measurement of dabigatran trough concentration in patients at least once after a steady-state has been reached, approximately after three days, to adjust the dose of dabigatran. More research is warranted.

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PHOTO QUIZ

Chronic diarrhoea in a 26-year-old man

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CASE REPORT

A 26-year-old man presented to the outpatient clinic of internal medicine with a three-month history of diarrhoea. He had loose, watery stools without mucous or blood up to five times a day. He had no fever or weight loss. His medical history was unremarkable and at presentation he was not on any medication. Social anamnesis revealed that he had homosexual anal receptive contacts.

At physical examination, the abdomen had positive bowel sounds and was soft and non-tender without palpable masses or organomegaly. Additional general physical examination also reveiled no abnormalities. Renal, liver and electrolyte profiles, blood count and white blood cell differential were within normal ranges. Diagnostic tests revealed no evidence for hyperthyroidism or celiac disease. Faecal cultures were negative for bacteria and parasites. Sexually transmitted disease screening, including a rectal swab for *C. trachomatis*, and HIV screening were negative. Finally, the patient underwent colonoscopy. No abnormalities were seen macroscopically, but histological examination of random colon biopsies showed colonic crypts with a thick 'fuzzy' brush border (*figures 1 and 2*).

WHAT IS YOUR DIAGNOSIS?

See page 317 for the answer to this photo quiz.

Figure 1. *Colonic biopsy showing colonic epithelium with a thick brush border (H&E x 100)*

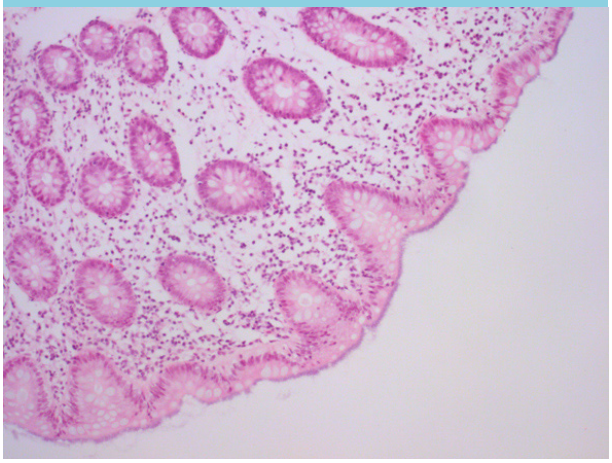
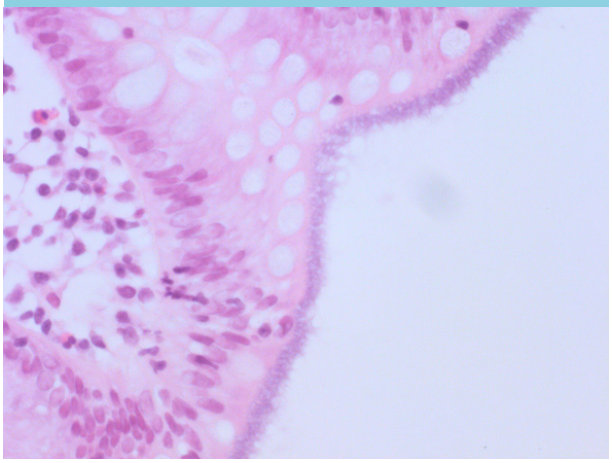


Figure 2. *Luminal surface with a thick 'fuzzy coating' (H&E x 400)*



ANSWER TO PHOTO QUIZ (PAGE 316)

CHRONIC DIARRHOEA IN A 26-YEAR-OLD MAN

DIAGNOSIS

Intestinal spirochetosis.

Intestinal spirochetosis is defined as colonisation of the colon or appendix by the anaerobic spirochetes *Brachyspira aalborgi* or *Brachyspira pilosicoli* (first described in the 17th century by Antoni van Leeuwenhoek).[1] Reported prevalence is 2-7% in Western countries, but rises to 54% in HIV-positive patients and those with homosexual contacts.[2] There is controversy about whether these spirochetes are commensals or pathogens. However, invasion of colonic epithelium by spirochetes, in patients with anal receptive contacts induced through microtrauma, leads to destruction of microvilli. Patients may complain of abdominal pain, constipation, bloody stools or diarrhoea. Because spirochetes are very difficult to culture and usually no macroscopic abnormalities are seen in colonoscopy, the diagnosis is made by histological examination of colon biopsies. A 'fuzzy' line of spirochetes is seen at the epithelial surface. Immunostaining shows a cross-reaction with *B. burgdorferi* and *Treponema pallidum*.[3] Anti-microbial treatment can relieve symptoms by eliminating spirochetes, which leads to recovery of microvilli. Spontaneous recovery has also been described.[4] Because our patient had debilitating symptoms, he was prescribed 500 mg metronidazole three times a day for one week, after which his symptoms completely resolved.

ACKNOWLEDGEMENTS

Credits go to Dr. Natté, pathologist, for providing the PA images.

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PHOTO QUIZ

A 43-year-old woman with a quadriparesis

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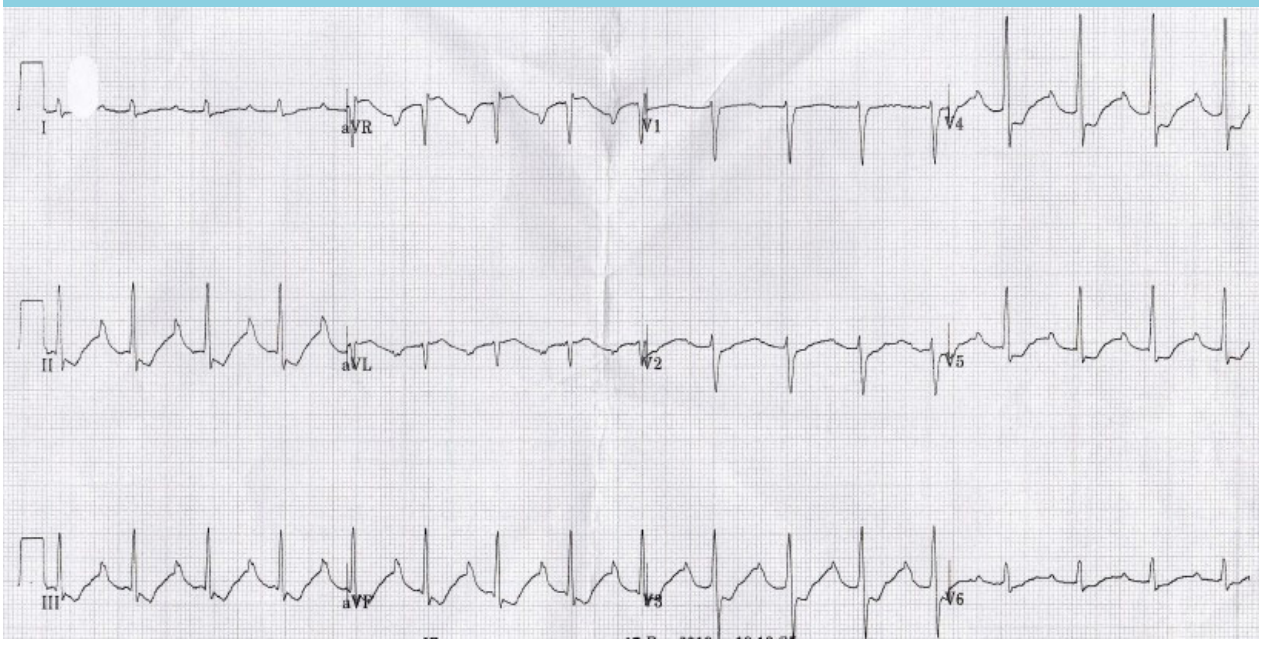
A 43-year-old woman presented to the emergency department with progressive weakness. Her medical history included the diagnosis of Crohn´s disease with multiple surgical procedures because of rectovaginal fistulas, a subtotal colectomy and terminal ileostomy. She required daily potassium chloride and fluoxetine. On presentation her partner carried her because weakness impeded her from walking. She complained of speaking difficulties, cramping sensation in her hands, stomach pain and vomiting with almost no intake in the last three days together with a fully productive stoma. In the foregoing days, she kept dropping things and she noticed having trouble walking. There was no history of traumatic injury. Physical examination revealed a cachectic woman with minimal diffuse abdominal tenderness. On neurological examination she could barely rotate her head. She experienced extreme difficulty lifting her arms. Examination of the legs also showed paresis with absence of tightening proximally and weakness distally. Reflexes were absent bilaterally in the upper and lower extremities. ECG showed a first-degree AV block with ST elevation in aVR and ST depression in several leads (*figure 1*). She worsened during her stay in the emergency department as she developed evident swallowing difficulties and progressed to imminent aspiration after a little sip of water.

WHAT IS YOUR DIAGNOSIS?

See page 319 for the answer to this photo quiz.

Figure 1. *ECG showing a first-degree AV block with ST elevation in aVR and ST depression in several leads*



ANSWER TO PHOTO QUIZ (PAGE 318)

A 43-YEAR-OLD WOMAN WITH A QUADRIPARESIS

DIAGNOSIS

When the results of the serum biochemistries came back, they showed a metabolic acidosis, magnesium 0.57 mmol/l and potassium 1.4 mmol/l with the latter being responsible for the symptomatology and ECG changes. Multiple factors attributed to the hypokalaemic state of this patient. Firstly, vomiting (due to Crohn's and fluoxetine) caused a potassium loss that was more than she could replenish with oral intake. Secondly, potassium was lost through her high-output stoma (> 2 l/day, for three consecutive days).[1] It is well known that a high-output stoma can cause metabolic disturbances. However, articles reporting about hypokalaemia of this magnitude due to high-output stomas are scarce.

The patient was admitted to the high care unit and given potassium and magnesium chloride using a central and peripheral catheter and was tube-fed, because she was too weak to swallow. The fluoxetine was stopped, as it is known to induce vomiting. The serum potassium levels stabilised during the following 12 hours with her paresis resolving quickly. She was discharged on day three after admission, with a complete recovery.

This patient had a life-threatening periodic hypokalaemia quadriparesis as a result of metabolic disturbances caused by, among other things, a high-output stoma with Crohn´s disease. The purpose of this article is to create awareness amongst internal medicine and emergency physicians and it should help them to be perceptive of patients with a high risk for metabolic disturbances and thus prevention of these conditions.

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PHOTO QUIZ

A medical cause for fifty shades of grey

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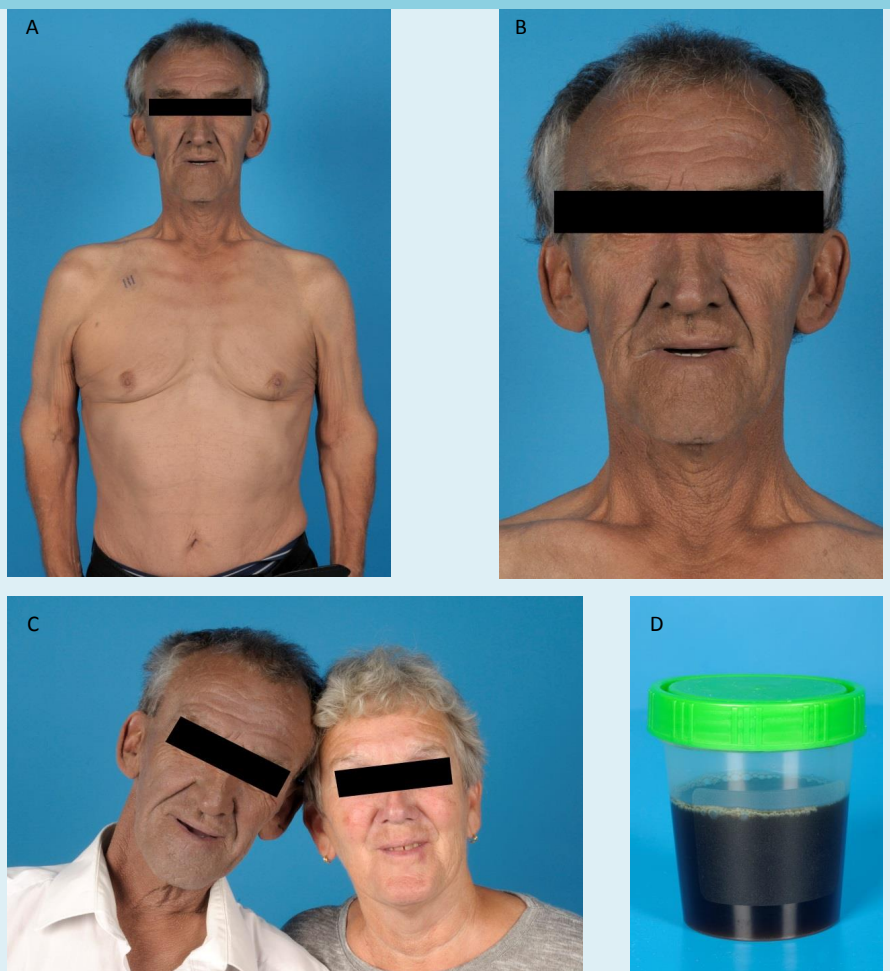
CASE REPORT

A 62-year-old patient presented with abdominal discomfort, weight loss, discoloration of the skin, and dark urine (*figure 1*). His medical history revealed achondroplasia. Physical examination showed a short stature due to achondroplasia, a remarkable blue-grey skin discoloration most pronounced in the sun exposed skin, pathological lymphadenopathies of the right axilla, an enlarged liver and a scar on his back after a wide excision of a skin lesion performed 20 years ago, according to the patient.

WHAT IS YOUR DIAGNOSIS?

See page 321 for the answer to this photo quiz.

Figure 1. *A,B: Blue-grey discoloration most pronounced in the sun-exposed skin. C: The patient and his sister (same parents). D: The patient's urine*



ANSWER TO PHOTO QUIZ (PAGE 320)

A MEDICAL CAUSE FOR FIFTY SHADES OF GREY

DIAGNOSIS

The wide local excision performed 20 years ago turned out to be because of melanoma. CT imaging showed right axillary lymphadenopathy, diffuse metastases in liver, adrenal glands, lungs and bones. Histological exam of an axillary lymph node biopsy revealed the diagnosis of metastatic melanoma. Mutation analysis revealed a BRAF V600E mutation, and the patient started on the BRAF inhibitor vemurafenib (960 mg twice daily) in September 2015.

The blue-grey discoloration of the skin, most pronounced in sun-exposed area, is called diffuse melanosis cutis. It is a rare symptom of metastatic melanoma, often accompanied with melanuria (77%).[1] Patients with melanosis cutis have a poor prognosis with a life expectancy that seldom exceeds 3-4 months.[1] The pathophysiological mechanisms are not certain; the hypothesis is that melanin precursors and melanin are released from melanoma metastases resulting in deposition of melanin in tissues leading to skin discoloration and melanuria.[1]

To our knowledge this is the third case reporting on a patient with diffuse melanosis cutis in the setting of BRAF V600E metastatic melanoma[2,3] and the second patient to be treated with a BRAF inhibitor.[3]

The described patient is still alive ten months after presentation with diffuse melanosis cutis. The best response to vemurafenib, assessed on CT scan, was stable disease with some lesions showing signs of regression and some lesions showing minimal growth. To our knowledge, there is no mention in the literature as to whether a change in discoloration of the skin and urine can be used as an outcome measure for response to treatment. The patient's skin and urine colour were documented with follow-up photographs, but the colour did not change during treatment. In the case described by Minocha et al.[3] the patient developed progressive disease after five months of dabrafenib after which he was treated with two cycles of ipilimumab 3 mg/kg with an 15-month interval. The treatment effects in these two cases are comparable with the median progression-free survival of six months seen with BRAF inhibitor treatment in metastatic melanoma in general.[4] The course of our patient clearly demonstrates that with the use of the currently available, novel-targeted therapies, melanosis cutis may no longer be the dismal prognostic indicator it was in the past. Therapy for this entity should be similar to the therapy given for metastatic melanoma in general.

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LETTER TO THE EDITOR

More takotsubo syndrome in Guillain-Barré syndrome

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To the Editor,

With interest we read the article by Boon et al. about a 39-year-old female with Guillain-Barré syndrome (GBS) requiring artificial ventilation who developed takotsubo syndrome (TTS) shortly after intubation.[1] We have the following comments and concerns.

TTS was not only associated with the eight cases listed in Boon's article.[1] If other terms describing takotsubo syndrome, such as stunned myocardium, stress cardiomyopathy, broken heart syndrome, or reversible (transient) cardiomyopathy, are considered and also atypical types of GBS are included, takotsubo syndrome has been reported in many more cases (*table 1*). The axonal type of GBS was associated with stunned myocardium in a 27-year-old Chinese female, who recovered under immunosuppression and plasmapheresis.[2] TTS was additionally reported in a 59-year-old Indian male with GBS and dysautonomia who recovered under immunomodulating therapy and heart failure treatment within three months.[3] A further case of a 82-year-old female with classical GBS was reported from the USA.[4] This patient recovered completely under plasma exchange but the cardiac therapy was not mentioned.[4] In the case of a 33-year-old Filipino male, TTS was the initial presentation of GBS.[5] TTS recovered completely under diuretics exclusively and GBS resolved upon immunoglobulins.[5] Possibly, also the case of a 68-year-old female with GBS reported by Goldmann in 2006 describes TTS since myocarditis was only suspected and not confirmed by endomyocardial biopsy.[6] Together with Boon's cases, at least 13 cases of GBS-associated TTS have been reported.

Triggers of TTS are usually fear or pain. Fear may be spontaneous or triggered. Triggered fear may be endogenous (e.g. another illness) or exogenous (e.g. aggression, pain). The authors do not mention any trigger for the TTS. What was the trigger of TTS in the presented case? Was it the stress of respiratory insufficiency and dyspnoea prior to intubation? Was there another fearful event or did she experience severe pain prior to respiratory insufficiency?

Catecholamines are contraindicated in TTS. Why did the patient receive norepinephrine? Was it because of

Table 1. *Cases of Guillain-Barré syndrome in which takotsubo syndrome was described in addition to the eight cases reported by Boon et al.*[1]

Reference	Age	Sex	GBS type	GBS therapy	TTS therapy	Outcome
Magid-Bernstein 2016[2]	27	F	Axonal	PE	None	Full recovery
Renjen 2014[3]	59	M	Mixed	IG, PE	β-blockers, diuretics, ACEI	Full recovery
Fugate 2009[4]	82	F	Demyelinating	PE	Not mentioned	Full recovery
Rousseff 2010[5]	33	M	Demyelinating	IG	DR	Full recovery
Goldman 2006*[6]	68	F	Demyelinating	IG	DR	Full recovery

IG = immunoglobulins; PE = plasma exchange; ACEI = angiotensin-converting-enzyme inhibitors; * = originally diagnosed as myocarditis.

unawareness of the diagnosis? Did the TTS further worsen under this treatment?

Overall, this interesting case adds to the understanding of GBS as a trigger of TTS. Since TTS in GBS may significantly determine the outcome of these patients, it is essential to diagnose TTS instantly by taking chest pain seriously and initiating creatine kinase, troponin, and proBNP determination, ECG recordings, echocardiography and appropriate cardiac treatment. Myocarditis needs to be excluded before diagnosing TTS Whether immunomodulation improves or worsens, the outcome of TTS remains questionable.

DISCLOSURE

There are no conflicts of interest.

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LETTER TO THE EDITOR

A continuous infusion of etoposide and doxorubicin for refractory MAS management

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To the Editor,

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of adult-onset Still's disease (AOSD) without optimal treatment.[1] Here, we report a case of MAS caused by AOSD, which was effectively treated by a 96-hour continuous infusion of etoposide and doxorubicin after the patient failed to respond to the traditional approach to treatment.

A previously healthy 23-year-old female was admitted with complaints of hyperpyrexia in 2013. Laboratory studies showed severe anaemia and elevated white blood cell count (neutrophils at 91%), increased erythrocyte sedimentation rate, hyperferritinaemia, and normal alanine aminotransferase (*table 1*). Bone marrow examination revealed no haemophagocytosis. Three days later, she developed a generalised rash with high fever, but negative in blood culture, despite the fact that ciprofloxacin and imipenem were administered aggressively. Further lab tests, including brucellosis, tuberculosis, Epstein-Barr virus, cytomegalovirus, anti-nuclear antibodies and rheumatoid factor, all turned out to be negative. No abnormalities were found in abdominal and superficial lymph nodes by ultrasonography. The patient was diagnosed with AOSD based on the Yamaguchi criteria and was administered high-dose methylprednisolone (1000 mg/day) and intravenous immunoglobulins (0.5 g/kg/day) for three days as suggested from a previous report,[2] which alleviated the fever and significantly improved the polyarthralgia. However, the fever recurred, and the serum ferritin increased when the methylprednisolone was tapered. At the same time, splenomegaly together with elevated triglyceride and sCD25 was observed

Table 1. *Variations of laboratory tests during the treatment of the refractory MAS secondary to AOSD*

Days after admission									
	+1	+3	+5	+20	+31	+36	+52	+85	+245
WBC (3.5-9.5×10⁹/l)	21.8	11.1	8.2	6.6	4.6	4.1	3.1	8.7	6,4
Haemoglobin (120-160 g/dl)	51	80	82	102	96	108	118	126	124
Platelets count(125-350×10⁹/l)	423	389	325	363	188	423	325	285	275
ESR (4-20 mm/h)	145	128	129	57	27	83	75	28	9
Triglyceride (0.56-1.7 mmol/l)	1.55	1.09	3.85	1.23	1.08	2.97	1.15	1.39	1.03
ALAT (0-40U/l)	11.2	48	154	27.3	52	56	39	31	10.9
Ferritin (21-270 ng/ml)	33,097	13,055	59,000	4430	2609	49,466	1291	316	158
Max temperature(°C)	39.8	38.5	40.1	37.8	37.6	39.7	37.5	36.5	36.5
Treatments*	HDMP+IVIG		VP16+DEX+CSA			VP16+ADM for 96 hours		DEX+CSA	

ALAT = alanine aminotransferase; ESR = erythrocyte sedimentation rate; *HDMP = high-dose methylprednisolone; HLH-2004 = haemophagocytic lymphohistiocytosis 2004 guidelines; IVIG = intravenous immunoglobulins; WBC white blood cell count. VP16+DEX+CSA: the standard treatment of HLH-2004, including etoposide (100 mg/m² per dose, twice weekly), dexamethasone (10 mg/m²/day), and cyclosporine (2.5 mg/kg/day). VP16+ADM for 96 hours: 96 hours of continuous infusion of etoposide and adriamycin; DEX+CSA: maintenance according to the HLH-2004.

with normal coagulation screening tests and natural killer cell activity (*table 1*). So the patient was diagnosed with MAS secondary to AOSD. Fever and splenomegaly were subsided under immunosuppressive therapy following the haemophagocytic lymphohistiocytosis 2004 guidelines[1] (*table 1*). However, the patient endured a flare-up of disease at the end of week 4. The effectiveness of the continuous infusion schedule in lymphoma inspired us to use the protocol to suppress excessive activated immune cells maximally [3]. A 96-hour continuous infusion of etoposide (50 mg/m²/day) and doxorubicin (10 mg/m²/day) was introduced biweekly. During the following course, her condition improved significantly without reactivation of the rheumatoid disorder (*table 1*).

High ferritin level is a typical manifestation of AOSD; however, hyperferritinaemia (> 10,000 ng/ml) is more suggestive of MAS secondary to AOSD. In this case, the patient had recurrent hyperferritinaemia and met five of the eight criteria required for the diagnosis of haemophagocytic lymphohistiocytosis or MAS. MAS should be diagnosed early and treated with immunosuppression drugs immediately. However, we have few choices in patients refractory to or intolerant of etoposide. Some monoclonal antibodies, such as daclizumab, infliximab, and adalimumab either introduced solo or in combination with etoposide showed some benefits in some refractory cases.[1] Unfortunately, those monoclonal antibodies were not available in China. In our case, we found that a 96-hour continuous infusion of etoposide and doxorubicin was safe and effective in the patient with refractory MAS secondary to AOSD. Etoposide may eliminate activated T cells selectively and suppress inflammatory cytokine production more efficiently as it does in lymphoma. It was proposed that extending drug exposure may enhance cell killing by modulating the cell cycle and apoptosis.[4]

In conclusion, a continuous infusion of etoposide and doxorubicin may be a safe and effective treatment alternative for patients with MAS secondary to AOSD.

DISCLOSURES

There is no conflict of interest.

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