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PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE



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VAN ZUIDEN COMMUNICATIONS

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# The Journal of Medicine

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**Editorial office 'The Netherlands Journal of Medicine'**
Geeralien Derksen-Willemsen
Radboud University Nijmegen Medical Centre
Department of General Internal Medicine 463
PO Box 9101, 6500 HB Nijmegen
The Netherlands
Tel.: +31 (0)24-361 04 59
Fax: +31 (0)24-354 17 34
E-mail: g.derksen@aig.umcn.nl
http://mc.manuscriptcentral.com/nethjmed

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Woodcut by Camiel Andriessen. For details about the artist, her work and how to order see elsewhere in this journal.



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EDITORIAL

# Announcements from the Editorial Board of the Netherlands Journal of Medicine

**A.F.H. Stalenhoef**

Editor-in-Chief, on behalf of the Editors

The editorial staff of the Netherlands Journal of Medicine, residing in Nijmegen for the last five years, has moved the Journal into the electronic era with the expectation that this would improve its accessibility and quality. From the summer of 2006 onwards, all full text articles published in the Journal have become freely accessible online.[1] As a consequence, accessing and downloading articles from the Journal via PubMed is easy and convenient and the number of hits easily exceeds 3000 every month.[2] In addition, we implemented an online submission and reviewing system in February of 2006, which not only enhanced the efficiency of the editorial workflow, but also attracted more articles, especially from abroad. This forced the editorial board to become much more selective in accepting papers, leading to a rejection rate of nearly 40% of submitted papers in 2006. More efficient handling of submissions last year shortened the time from submission to the final decision from an average of 98 days to less than 60 days in nearly 90% of the submissions (*figure 1*).[3]

The number and categories of articles submitted to the Journal in 2006 are listed in *table 1*.

In order to further decrease the circulation time of submissions, we need the help of our readers in reviewing submitted papers at short notice. Therefore, we invite (especially young) colleagues to apply as potential reviewers to achieve this goal. Those interested can contact the editorial office at g.derksen@aig.umcn.nl

In this new year, a couple of changes will take place.[4] First of all, Professor Paul Smits has resigned as Associate Editor of the Journal because of time constraints due to increasing managerial obligations since he recently became Chairman of the Division of Biomedical and Evaluative Sciences and Primary Care. The editorial staff is grateful for his valuable contribution to the editorial work in the last five years. We are pleased that we found Professor Jack Wetzels (*figure 2*) willing to join the editorial staff. Jack Wetzels (1954) is

**Table 1.** *Submissions to the Netherlands Journal of Medicine in 2006*

| Manuscript type | N | % |
|---|---|---|
| Case reports | 94 | 40.9 |
| Original articles | 58 | 25.2 |
| Reviews | 28 | 12.2 |
| Photo quizzes | 28 | 12.2 |
| Letters | 9 | 3.9 |
| Special reports | 6 | 2.6 |
| Editorials | 5 | 2.2 |
| Notes | 2 | 0.9 |
| | **230** | **100** |

**Figure 1.** *Time from submission to decision*

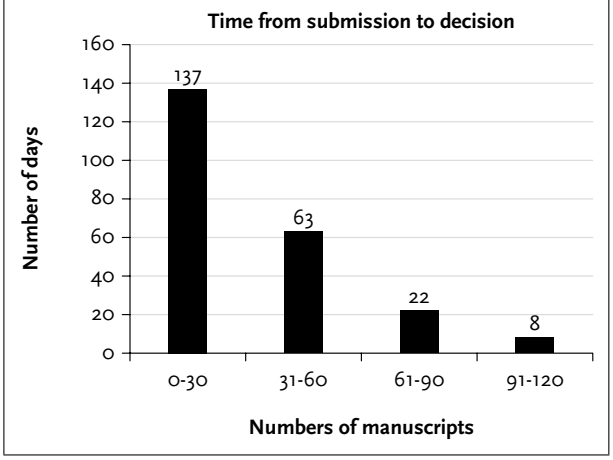


**Figure 2.** *New Associate Editor Professor Jack Wetzels*

Professor of Nephrology at the Department of Nephrology of the Radboud University Medical Centre, Nijmegen.

Secondly, after five years of art on the front cover, the artists have decided to stop their contribution to the Journal. Although we regret this enormously, we respect their decision. An exhibition of the art covers of the last two years is planned at our University later this year. We will replace the art covers by illustrations selected from photo quiz submissions starting in May of this year.
Of interest, the Journal is moving into its 50th year of publication! We would therefore like to pay attention to the history of the Journal and we have approached former Editors to write about their experiences with the Journal and these contributions will be published in the course of the year 2008.

With the help of our readers, the editors will continue to try to improve the quality of the Journal and finally break the Impact Factor barrier of 1, which is coming closer. This is the goal that we have set as editors for this year. We wish you a very healthy and productive new year!

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EDITORIAL

# The ups and downs of sirolimus in kidney transplantation, and the importance of reporting negative findings

**T. van Gelder**

Departments of Internal Medicine and Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands, tel.: +31 (0)10-463 32 02, e-mail: t.vangelder@erasmusmc.nl

We all know that trials with a positive outcome are more likely to be reported than trials with an inconclusive or negative outcome.[1] For studies that are prematurely discontinued, either for safety reasons, or for lack of efficacy of the medicinal product involved, publication of the outcome of the study is even less likely. However, for assessing the efficacy and safety of a drug it is imperative to consider the outcomes of all clinical trials. Inefficient or unsafe therapies may be retried by other investigators, unaware of the outcome of previous trials. Furthermore, individuals who participate in clinical trials typically provide consent in the belief that they are contributing to medical knowledge. But if the knowledge is never reported, the trust between patients and investigators is damaged. A comprehensive register of initiated trials has been proposed to reduce publication bias.[2] Registers will allow identification of unpublished studies and the possibility to find out more about these trials, which is especially crucial for systematic reviews of randomised trials. A trial register has also been initiated in the Netherlands.[3]
The importance of reporting negative findings is nicely exemplified by the paper from Van den Akker *et al.* in this issue of the Journal.[4] Their experience with a sirolimus-based immunosuppressive treatment regimen may serve as a red flag for other professionals in the field of solid organ transplantation. What did they do, what were their findings, and how did they decide to explore this treatment in their patients?
For the prevention of acute rejection after kidney transplantation the calcineurin inhibitors cyclosporin and tacrolimus have been, and still are, the cornerstone of immunosuppressive therapy. However, long-term use of calcineurin inhibitors is thought to be associated with an increased risk of cardiovascular disease and chronic renal allograft dysfunction.[5] Sirolimus blocks T-lymphocyte activation by a mechanism distinct from calcineurin inhibitors. Therefore, it may be expected that sirolimus would display a safety profile without the nephrotoxicity that is associated with the use of calcineurin inhibitors.
Two phase III randomised trials with sirolimus were conducted in human renal transplantation in 1996-1997. In these studies 2 or 5 mg of sirolimus a day was compared with either placebo (Global Study)[6] or azathioprine (United States Study)[7] in combination with full exposures to cyclosporine and corticosteroids. In both studies the sirolimus-treated patients had significantly lower incidences of biopsy-confirmed acute rejection than the control arm, but creatinine clearance values were reduced in the sirolimus groups. These trials raised the concern that sirolimus had a direct adverse effect on renal function, or exacerbated the nephrotoxicity of cyclosporine. It now appears that both pharmacokinetic and pharmacodynamic mechanisms are implicated, and subsequent experience has shown that cyclosporine dose reduction or discontinuation mitigates these effects.[8,9]
Other concerns with the use of sirolimus early after transplantation are prolongation of recovery from delayed graft function,[10] lymphocele formation and impaired wound healing,[6,7] and proteinuria following conversion from other immunosuppressive drugs to sirolimus.[11]
As an alternative to combining sirolimus with reduced-dose calcineurin inhibitor, or elimination of cyclosporine within the first six months after transplantation, a third option is complete avoidance of calcineurin inhibitors. Following two earlier studies applying a calcineurin inhibitor-free protocol,[12,13] Flechner *et al.* compared a sirolimus-based protocol with cyclosporin-based immunosuppression, in combination with basiliximab, mycophenolate mofetil and steroids.[14] This small study (n = 61) has received a lot of attention, as the investigators not only succeeded in achieving a very low incidence of rejection in the sirolimus-treated patients (6.4%), creatinine clearance at two years was also significantly better.[15] With the expectation that calcineurin avoidance would indeed lead

to better renal function and longer graft survival, many centres implemented calcineurin inhibitor-free protocols either as part of investigator-initiated studies, or for daily patient care.

The experience from Van den Akker *et al.*, described in this issue of the Journal, challenges this hope.[4] In their prematurely stopped study they found a very high rejection incidence (70%) in the first ten patients treated with a calcineurin inhibitor-free protocol. Subsequently Van den Akker *et al.* decided to change the protocol to better reflect the Flechner regimen, and increased the overall amount of immunosuppression. With this approach rejections no longer occurred, but toxicity was unacceptable. Obviously, the reader of this paper is discouraged from trying to initiate calcineurin inhibitor-free kidney transplantation protocols. The so far unpublished results of the Symphony study, which included 1645 (!) patients, also shed some new light on the optimistic Flechner data. In the Symphony study conventional immunosuppression (cyclosporine, mycophenolate mofetil and steroids), was compared with three low-toxicity regimens, one of which consisted of treatment with basiliximab, sirolimus, mycophenolate mofetil and steroids.[16] In this calcineurin inhibitor-free arm (n = 399) the incidence of biopsy-proven acute rejection was 37.2%, three times higher than that in the low-dose tacrolimus arm (12.3%). These results will convince most physicians not to embark on calcineurin inhibitor-free protocols.

This does not mean there is no future for sirolimus. There is still a need to reduce the burden of calcineurin inhibitor-related nephrotoxicity. And sirolimus still carries the promise of a reduced risk for developing cancer.[17] Other strategies need to be explored. Possibly, a delayed introduction of sirolimus in the second or third quarter after transplantation is the way to go. This would maintain the early benefits of calcineurin inhibitor therapy in preventing acute rejection episodes, and at the same time allow for improving, or stabilising, renal function thereafter.

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REVIEW

# Evidence-based guideline on management of colorectal liver metastases in the Netherlands

**S. Bipat[1*], M.S. van Leeuwen[2], J.N.M. IJzermans[3], E.F.I. Comans[4], A.S.Th. Planting[5], P.M.M. Bossuyt[6], J-W. Greve[7], J. Stoker[1]**

[1]Department of Radiology, Academic Medical Centre, Amsterdam, [2]Department of Radiology, University Medical Centre Utrecht, [3]Department of Surgery, Erasmus Medical Centre, Rotterdam, [4]Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam, [5]Department of Medical Oncology, Erasmus Medical Centre, Rotterdam, [6]Department of Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam, [7]Department of Surgery, Maastricht University Hospital, [*]corresponding author S. Bipat, Department of Radiology, Academic Medical Centre, Amsterdam, the Netherlands, e-mail: s.bipat@amc.uva.nl

## ABSTRACT

**A Dutch national evidence-based guideline on the diagnosis and treatment of patients with colorectal liver metastases has been developed. The most important recommendations are as follows. For synchronous liver metastases, spiral computed tomography (CT) or magnetic resonance imaging (MRI) should be used as imaging. For evaluation of lung metastases, imaging can be limited to chest radiography. For detection of metachronous liver metastases, ultrasonography could be performed as initial modality if the entire liver is adequately visualised. In doubtful cases or potential candidates for surgery, CT or MRI should be performed as additional imaging. For evaluation of extrahepatic disease, abdominal and chest CT could be performed. Fluorodeoxyglucose positron emission tomography could be valuable in patients selected for surgery based on CT (liver/abdomen/chest), for identifying additional extrahepatic disease. Surgical resection is the treatment of choice with a five-year survival of 30 to 40%. Variation in selection criteria for surgery is caused by inconclusive data in the literature concerning surgical margins <10 mm, presence of extrahepatic disease and the role of (neo)adjuvant therapy. To minimise variation in selection criteria, selection should be performed according to this guideline and preferably in qualified centres. If resection is not possible due to extensive disease, palliative chemotherapy is recommended. Systemic chemotherapy with fluoropyrimidine first-line chemotherapy (5-FU/Leucovorin) combined with irinotecan or oxaliplatin should be considered as standard regimens. Radiofrequency ablation, isolated hepatic perfusion, portal vein embolisation, and intra-arterial chemotherapy are considered experimental and should only be performed as part of a clinical research protocol.**

## KEYWORDS

Guideline, liver metastases, diagnosis, treatment, colorectal neoplasms

## INTRODUCTION

Colorectal cancer is the second leading cause of cancer-related deaths in the Netherlands with an incidence of 9900 and 4400 deaths in 2003 according to the Association of Comprehensive Cancer Centres.[1] Approximately 50 to 60% of patients with colorectal cancer eventually develop liver metastases. As there are variations in the therapeutic strategies for these patients, the optimal therapy should be determined on an individual basis. A Dutch survey on the diagnostic and therapeutic work-up of patients with colorectal liver metastases performed in 2004 showed substantial variation between different centres in both diagnostic work-up and treatment. The most important points of concern according to the responders of this survey were the absence of a national guideline for diagnosis and treatment of patients with colorectal liver metastases and the absence of a registration system.[2]

## METHODS

To develop a national evidence-based guideline, a working group was established representing the disciplines involved in this field, including surgeons, medical oncologists, radiologists, gastroenterologists and nuclear medicine specialists. All specialists were mandated by their respective health professional organisations. A list of the members of the working group is presented in *appendix 1*.

We performed literature searches in the Cochrane, Medline, CANCERLIT, EMBASE, CINAHL and Web of Science databases from 1992 to 2005 for different questions. The search strategies are described in *table 1*. Literature searches were performed for:

1. Diagnostic accuracy of computed tomography (CT), magnetic resonance imaging (MRI), 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in the detection of liver metastases and for detection of extrahepatic lesions; no search was performed for the diagnostic accuracy of ultrasonography (US), as this modality has a low accuracy;
2. The diagnostic accuracy of diagnostic laparoscopy in the detection of liver metastases and for detection of extrahepatic lesions;
3. The selection criteria on which surgery is based;
4. The effectiveness of (neo)adjuvant chemotherapy;
5. The role and effectiveness of the experimental therapeutic options such as portal vein embolisation, ablation techniques and isolated hepatic perfusion; the effectiveness of the different chemotherapeutic regimens used;
6. The role of follow-up after treatment of colorectal liver metastases.

All evidence was collected, discussed and categorised by the working group according to general systems used in evidence-based medicine (*table 2*). Based on the relevant evidence and taking into account factors such as experience and availability, recommendations were formulated for daily practice. These recommendations with corresponding evidence were sent to all the disciplines involved for comments, remarks and approval; all disciplines responded with minor comments, remarks and suggestions and approved the final draft of the

**Table 1.** *Search strategies*

**DIAGNOSIS**

**MEDLINE**
Colorectal Neoplasms [MESH]) AND (Liver neoplasms [MESH]) AND ((Laparoscopy [MESH]) OR (Tomography, Emission-Computed [MESH]) OR (magnetic resonance imaging [MESH]) OR (Tomography, X-Ray Computed [MESH]) OR (ULTRASONOGRAPHY [MESH])) AND ((sensitivity and specificity [MESH]) OR (specificity [WORD]) OR (false negative [WORD]) OR (diagnosis [SH]) OR (diagnostic use [SH]) OR (detection [WORD]) OR (accuracy [WORD]))

**EMBASE**
(Colorectal Cancer [MESH]) AND (Liver metastasis [MESH])

**CINAHL/SUMSEARCH**
(Colorectal Neoplasm [MESH]) AND ((Liver Neoplasms [MESH]) OR (Neoplasm Metastasis [MESH]))

**Web of Science/CANCERLIT/ COCHRANE**
(Colorectal cancer) AND ((liver metastases) OR (hepatic metastasis))

**TREAMENT**

**MEDLINE**
(Colorectal Neoplasms [MESH]) AND (Liver Neoplasms [MESH]) AND ((surgery [MESH]) OR (Hepatectomy [MESH]) OR (PERIOPERATIVE CARE [MESH]) OR (Catheter Ablation [MESH]) OR (Cryosurgery [MESH]) OR (Hyperthermia, Induced [MESH]) OR (Palliative Care [MESH]) OR (Drug therapy [MESH]) OR (Antineoplastic Agents [MESH]) OR (Infusions, Intra-Arterial [MESH]) OR (Perfusion, Regional [MESH]) OR (Radiotherapy [MESH])) AND ((Treatment outcome [MESH]) OR (Survival analysis [MESH] OR (Survival [MESH]) OR (Mortality [MESH]) OR (Morbidity [MESH]))

**EMBASE**
(Colorectal Cancer [MESH]) AND (Liver metastasis [MESH])

**CINAHL/SUMSEARCH**
(Colorectal Neoplasm [MESH]) AND ((Liver Neoplasms [MESH]) OR (Neoplasm Metastasis [MESH]))

**Web of Science/CANCERLIT/ COCHRANE**
(Colorectal cancer) AND ((liver metastases) OR (hepatic metastasis))

**Table 2.** *Levels of evidence based on the categories of literature*[*]

| | |
|---|---|
| **Level of evidence** | |
| **1** | Systematic review (A1) or at least two independently performed studies of category A2 |
| **2** | Systematic review (B1) or at least two independently performed studies of category B2 |
| **3** | 1 study of category A2, B2 or C |
| **4** | Expert opinion (category D) |
| **Categories of literature** | |
| **A1** | Systematic reviews of category A2 studies with consistent findings |
| **A2** | D: accuracy study (index test compared with reference test) of a high quality (prospectively performed with blinded interpretation of index test and reference test and large number of consecutive patients undergoing complete verification)<br>T: Randomised controlled trials of high quality (randomised, blinded, complete follow-up, similar baseline characteristics, intension-to-treat analysis) |
| **B1** | Systematic reviews of category B2 studies with consistent findings |
| **B2** | D: accuracy study (index test compared with reference test) with poor quality (missing the above mentioned characteristics)<br>T: Randomised controlled trial of low quality or other comparative studies such as nonrandomised, cohort and case-control studies |
| **C** | D: Noncomparative study (index test not compared with reference test)<br>T: Nonrandomised, cohort and case-control studies with poor quality or descriptive studies (non-comparative studies) |
| **D** | Opinion from expert committee or clinical experience |

**D = diagnosis; T = treatment**

[*] **Sackett DL, Strauss SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: How to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone 2000.**

guideline. All comments and remarks were incorporated in the final version of the guideline.

In this paper, on behalf of the working group, we report the recommendations with the corresponding evidence (including the level of evidence) for the diagnosis, treatment and follow-up of patients with colorectal liver metastases in the Netherlands.

## DIAGNOSIS

Beside medical history, physical examination and laboratory testing (e.g. carcinoembryonic antigen (CEA) measurements), imaging modalities such as transabdominal ultrasonography (US), CT, MRI and FDG-PET imaging play a major role in the selection of patients with liver metastases.[3-11] During the past ten years, improvements in the imaging modalities and changes in applications have been made.[6,7,10] Extensive research has been carried out on the diagnostic performance of US, CT, MRI, and FDG-PET for the detection of liver metastases. Another diagnostic technique playing a role in the evaluation of liver metastases is diagnostic laparoscopy. However, the optimal imaging staging strategy has not yet been defined.

Imaging plays a major role at the time of the diagnosis and treatment of the primary tumour (for detection of synchronous liver and lung metastases); during the follow-up after the treatment of the primary tumour (for detection of metachronous liver metastases) and for determining the resectability (detection of liver metastases and extrahepatic disease). The recommendations are described in the following paragraphs.

### At the time of initial diagnosis and treatment

1. To study baseline characteristics, a spiral CT or MRI of the liver should be performed instead of US, due to the low accuracy of US. Baseline CT or MRI are important not only for the detection or characterisation of liver lesions, but also for determining whether patients need adjuvant therapy. In case of doubt about the presence and characterisation of lesions, the CT or MRI examination should be repeated after three months. (Level of evidence: 4)
2. For the evaluation of the lungs, imaging can be limited to plain chest radiography, due to the low prevalence of lung metastases. CT provides a high sensitivity, but it should be noted that chest CT also gives more false-positives. In addition, in patients with negative chest radiography, the additional value of CT is limited.[12,13] (Level of evidence: 3)

### During follow-up and to determine resectability

1. For the detection of metachronous liver metastases, we recommend using CEA as marker if an elevated CEA level was measured at the time of detection of the primary colorectal tumour. For the evaluation of the liver, imaging may be limited to US if the entire liver is assessable. For follow-up no additional value of spiral CT or MRI to US has been demonstrated.[14] (Level of evidence 2) Because of its noninvasive character, low cost, and widespread availability, US is a valuable screening tool for the imaging of liver metastases. Moreover, US is highly efficient in helping to distinguish between two groups of patients with liver metastases: patients with diffuse metastases who are no longer eligible for curative treatment and patients with no or a limited number of metastases. In daily practice, therefore, US is often used as the initial imaging modality for the detection of metachronous liver metastases.[2]
2. If the liver cannot be evaluated properly by US, or the CEA elevation cannot be explained or the irresectability cannot be determined based on US, an additional spiral CT or MRI should be performed. MRI with gadolinium (Gd) or superparamagnetic iron oxide (SPIO) contrast medium and spiral CT with ≥45 g iodine have a comparable sensitivity for the detection of liver metastases.[15] (Level of evidence: 1) The choice between spiral CT with >45 g Iodine or MRI with contrast agent (Gd or SPIO) should, therefore, be mainly based on the local infrastructure (costs, availability and expertise).
3. The role of FDG-PET for the detection of liver metastases and determining the resectability is limited and should therefore not be performed routinely. In case of doubt concerning lesion characterisation on CT and MRI examination, an additional FDG-PET could be helpful, because in patients with a long interval between CT and FDG-PET or patients selected for additional FDG-PET, FDG-PET seems to be sensitive for the detection of liver metastases[2] and is therefore also used as additional modality in daily practice. (Level of evidence: 1)
4. The prevalence of extrahepatic disease (lung metastases and lymph node metastases) in patients selected for surgery based on extensive imaging is low. From a practical point of view, during the CT of the liver, additional CT of the abdomen could be performed for evaluation of the abdomen. There are no studies evaluating the additional role of abdominal CT for detection of extrahepatic disease.

   For the evaluation of the lungs, a chest CT could also be performed; however, chest CT provides a high number of false-positives and the additional value in patients with negative chest radiography seems to be low.[12,13] (Level of evidence: 3) Taking into account the low prevalence of lung metastases and the limited additional value of chest CT for evaluation of the lungs, imaging can be limited to plain chest radiography.
5. In patients selected for surgery after chest, liver and abdominal CT, an additional FDG-PET can be considered. FDG-PET seems to be sensitive for the detection of extrahepatic disease.[16] (Level of evidence: 1)

Moreover, the preliminary results of the POLEM study (randomised study: half of the patients selected for surgery based on abdominal, chest and liver CT underwent FDG-PET) showed that unnecessary laparotomy can be prevented in significantly more patients in the FDG-PET group. In the non-FDG-PET group 29% (14/49) underwent unnecessary laparotomy, while in FDG-PET group only 11% (5/48) underwent unnecessary laparotomy (p=0.02); in the FDG-PET group, surgery was cancelled in four patients after FDG-PET. However, these data are based on preliminary nine-month follow-up of 97 patients, while 150 patients are included in this study. (Report POLEM study, the Netherlands Organisation for Health Research and Development (ZonMw) grant 945-11-017).

## PET-CT

Hybrid PET-CT can be used for detection of liver metastases and extrahepatic disease when equipment and sufficient expertise is available. Studies have shown that accuracy rates of up to 98% can be achieved for the detection of liver metastases, extrahepatic disease and local recurrence in patients who have been treated for colorectal tumour.[17-19] (Level of evidence: 3)

## DIAGNOSTIC LAPAROSCOPY

There is no role for diagnostic laparoscopy in routine daily practice, due to its invasiveness, low prevalence of small subcapsular lesions and extrahepatic disease and absence of clinical consequences of small liver metastases, as these can generally be resected. The additional value of diagnostic laparoscopy in patients after extensive imaging also seems to be limited.[20,21] (Level of evidence: 3)

## ADDITIONAL EXAMINATION

1. If liver metastases seem to be resectable based on imaging examination, additional examination of the cardiopulmonary system should be performed to study the clinical condition of the patient. In general no cytological/ histological biopsies are performed.
2. If liver metastases based on imaging examination and the clinical condition of the patient seem to be irresectable, no cytological/histological biopsies should be performed to verify the diagnosis because of the increased risk of developing needle tract metastases.[22] Biopsies should only be performed if histopathology will have clinical consequences.

## SURGERY

Approximately 20% of patients with liver metastases are considered candidates for surgery, with a five-year survival of 30 to 40%.[23-26] Selection criteria for surgery are a residual liver volume of ≥30% after resection, the feasibility of an R0 resection (clear resection margin), limited or no presence of extrahepatic disease and adequate clinical condition of the patient. However, there is some variation in the prognostic factors such as the presence of extrahepatic disease, surgical margins <10 mm and the timing of the resection of synchronous liver metastases.[2] Neoadjuvant and adjuvant chemotherapy are usually administrated to increase the effectiveness of surgery.[27,28] The effectiveness of (neo)adjuvant chemotherapy is also unknown.

Recommendations based on the evidence found in the literature:

1. In patients with a normal functioning liver, at least 30% of the liver parenchyma should remain after surgery. Up to 70% of the liver volume can be removed in these patients with a normal functioning liver without risks of postoperative failure.[29-31] (Level of evidence: 3)
2. As there are no uniform results in the literature concerning a margin of <10 mm [32-36] (Level of evidence: 3) and due to the fact that the surgical margin cannot be accurately determined preoperatively, a surgical margin of ≥10 mm is recommended. Depending on the anatomic location, a margin of <10 mm is acceptable as long as a radical resection can be obtained.
3. Attention should be paid to the preoperative evaluation of extrahepatic disease, as patients with extrahepatic disease have a significantly worse prognosis compared with patients without extrahepatic disease.[37,38] (Level of evidence: 3)
   However, there is some controversial data on the consequences of the involvement of lymph nodes located near the liver hilum. Several papers report that this should not be considered an absolute contraindication for resection and an extended lymphadenectomy should be performed,[39,40] while in a systematic review only few five-year survivors after liver resection with involvement of hilum lymph nodes were reported.[41] In summary, there is no uniform evidence concerning the resection of lymph nodes in the hilum of the liver.
4. The presence of a limited number of lung metastases, without mediastinal lymph node involvement, is not considered an absolute contraindication for resection of liver metastases, as resection of a limited number of lung metastases can prolong long-term survival.[42-46] (Level of evidence: 3) Therefore, after radical surgery of the liver, subsequent lung surgery could be considered when only a limited number of lung metastases are found.

5. High age in a patient with good cardiopulmonary condition should not be a contraindication for liver resection for colorectal cancer metastases. In patients >70 years a median survival of up to 33 months and a five-year survival of up to 22% can be achieved.[47,48] (Level of evidence: 3)
6. Although patients with solitary metachronous liver metastases have a better survival compared with patients with synchronous metastases, the presence of synchronous liver metastases should not be a contraindication for surgery, as five-year survival of up to 31% can be obtained by resection of synchronous metastases.[49-51] (Level of evidence: 3)
7. Even though survival after simultaneous resection of colorectal cancer and liver metastases and resection of liver metastases after an interval of two to three months are comparable,[51,52] simultaneous resection should be avoided, due to the high complication rate. In addition, in two-thirds of patients major hepatic surgery is avoided, because of the detection of an increased number of hepatic or distant metastases after an interval of two to three months.[52] (Level of evidence: 3)
8. Repeat hepatectomy is advised in patients with new liver metastases after previous liver surgery for colorectal metastases, if the patient fulfils all criteria for resectability. Repeat liver resection for colorectal liver metastases is safe and in well-selected patients can provide prolonged survival after recurrence of colorectal liver metastases with limited mortality and morbidity rate.[53-59] (Level of evidence: 3)
9. Data on the effectiveness of (neo)adjuvant chemotherapy are controversial and we therefore recommend the use of (neo)adjuvant chemotherapy only in clinical research protocols. In a selected patient population, neoadjuvant chemotherapy with the more effective regimens (combination of 5-FU/LV with irinotecan or oxaliplatin) can induce response, making curative resection of previously irresectable liver metastases possible.[27,60-65] (Level of evidence: 3)

   The role of adjuvant chemotherapy after curative surgery is unclear and not advised routinely.[66-71] (Level of evidence: 2)

As there is a substantial variation in prognostic factors (see above), the working group recommends that:

1. Liver resection should be performed in centres with high experience level, where appropriate equipment is available and with enough experience in intensive care, anaesthesiology and interventional radiology. Administration of (neo)adjuvant chemotherapy should be limited to trials.
2. Registration of patients should be performed, also outside trials. Registration systems are important tools in evaluating indications for resection and results of resections.

## EXPERIMENTAL THERAPY

As most of the patients with liver metastases are not considered suitable for surgery, other treatment modalities such as ablative therapy, portal vein embolisation and isolated hepatic perfusion have been developed during the last decades.[72-82] However, there is no information available on the effectiveness of these modalities and the criteria for their application in the Netherlands.[2] The recommendations of the working group are given for each experimental therapy.

## PORTAL VEIN EMBOLISATION

Some patients not considered candidates for surgery due to insufficient remnant liver volume with increased risk of postoperative liver failure can undergo portal vein embolisation (PVE) of the liver parts to be resected. Portal vein embolisation results in atrophy of the embolised parts and hypertrophy of the remnant liver, reducing the risk of hepatic failure after extended hepatectomy. So far, only retrospective studies with long-term results[83,84] or prospective studies with short-term results in terms of success rate and complications[74,85-88] have been reported with, in general, favourable results/findings. (Level of evidence: 3) Moreover, small numbers of patients have been included in these studies. Due to the lack of data on long-term results, PVE should only be performed in trials, in centres with high experience and where clear-cut indications are defined.

## ABLATIVE THERAPY

Another treatment modality developed during the last decades for patients with liver malignancies is local ablation therapy. The principle of ablation is based on tumour destruction by applying heat (RFA or interstitial laser therapy) or cold (cryotherapy) or by chemical tumour destruction (ethanol injection).

1. No recommendations could be made on the role of laser ablation, due to the small number of studies evaluating long-term results of laser therapy.[89,90] (Level of evidence: 3)
2. The number of studies with long-term results on cryotherapy is limited. In comparison with RFA, cryotherapy has a higher complication rate (bleeding and infection) and more recurrence.[73,89,91] (Level of evidence: 3)
3. The use of ethanol injection for colorectal liver metastases is not advised, due to the small number of studies and the low response rate obtained.[92-94] (Level of evidence: 3)

4. RFA is the most promising technique for ablation purposes.[95-98] (Level of evidence: 3) This technique is highly effective for tumour destruction. However, it is not known whether RFA will prolong the survival of patients with extensive disease. In an ongoing randomised phase III study (CLOCC trial), the role of local treatment by RFA in patients with irresectable colorectal liver metastases is being studied. In this study one arm receives RFA combined with chemotherapy while the second arm receives only chemotherapy.
   Current evidence on the safety and efficacy of RFA for colorectal cancer liver metastases does not appear adequate and this experimental therapy should therefore only be performed as part of a clinical research protocol.

## ISOLATED HEPATIC PERFUSION

In patients with extensive nonresectable liver metastases, isolated hepatic perfusion (IHP) can be considered. IHP involves intraoperative perfusion of the isolated liver with extremely high-dose chemotherapy. The results of recent studies show that high response rates and considerable survival benefit can be achieved by IHP with different treatment strategies, including IHP with melphalan alone and melphalan combined with TNF-α or followed by monthly hepatic intra-arterial infusion of fluorodeoxyuridine (FUDR) and leucovorin. In these studies, IHP for colorectal liver metastases showed response rates of up to 74%, a median time to progression of up to 14.5 months and a median survival of up to 27 months.[75,99] (Level of evidence: 3)
IHP was first clinically applied over 40 years ago, but its technical complexity, the potential morbidity, toxicity rate and the lack of documented efficacy have probably prevented widespread use. Patient selection is important to ensure good results with minimal morbidity and mortality. Work to define the appropriate clinical groups is ongoing in the Leiden University Medical Centre and the Erasmus Medical Centre Rotterdam and therefore it is necessary to wait for the results of these studies.

## CHEMOTHERAPY

Most patients with extensive and nonresectable metastases are only eligible for systemic chemotherapy. The following recommendations for systematic chemotherapy can be made:

1. For systemic chemotherapy fluoropyrimidine first-line chemotherapy (either oral or systemic 5-FU/leucovorin) combined with irinotecan or oxaliplatin should be considered as standard regimens; however, the optimal regimens with either irinotecan or oxaliplatin are unknown. The effect of oral 5-FU prodrug monotherapy is comparable with intravenous bolus 5-FU regimens.[100-103] (Level of evidence: 1) Irinotecan or oxaliplatin combined with 5-FU/leucovorin increases the response and disease-free-survival compared with 5-FU/leucovorin alone.[104-106] (Level of evidence: 2)
2. In the absence of contraindications, bevacizumab could be added to the first-line chemotherapy. This has additional therapeutic value if bevacizumab is added to a fluoropyrimidine first-line chemotherapy regimen (higher response rate, disease-free and total survival).[107,108] (Level of evidence: 2)
3. An improvement in the field of chemotherapy is the development of regional (intra-arterial) chemotherapy.[109-111] With regional chemotherapy higher doses can be administrated and therefore higher tumour response rates could be achieved; however, the effectiveness in terms of disease-free survival and overall survival are yet unknown.[112] (Level of evidence: 1) Therefore, regional chemotherapy at this stage has no role in the routine management.

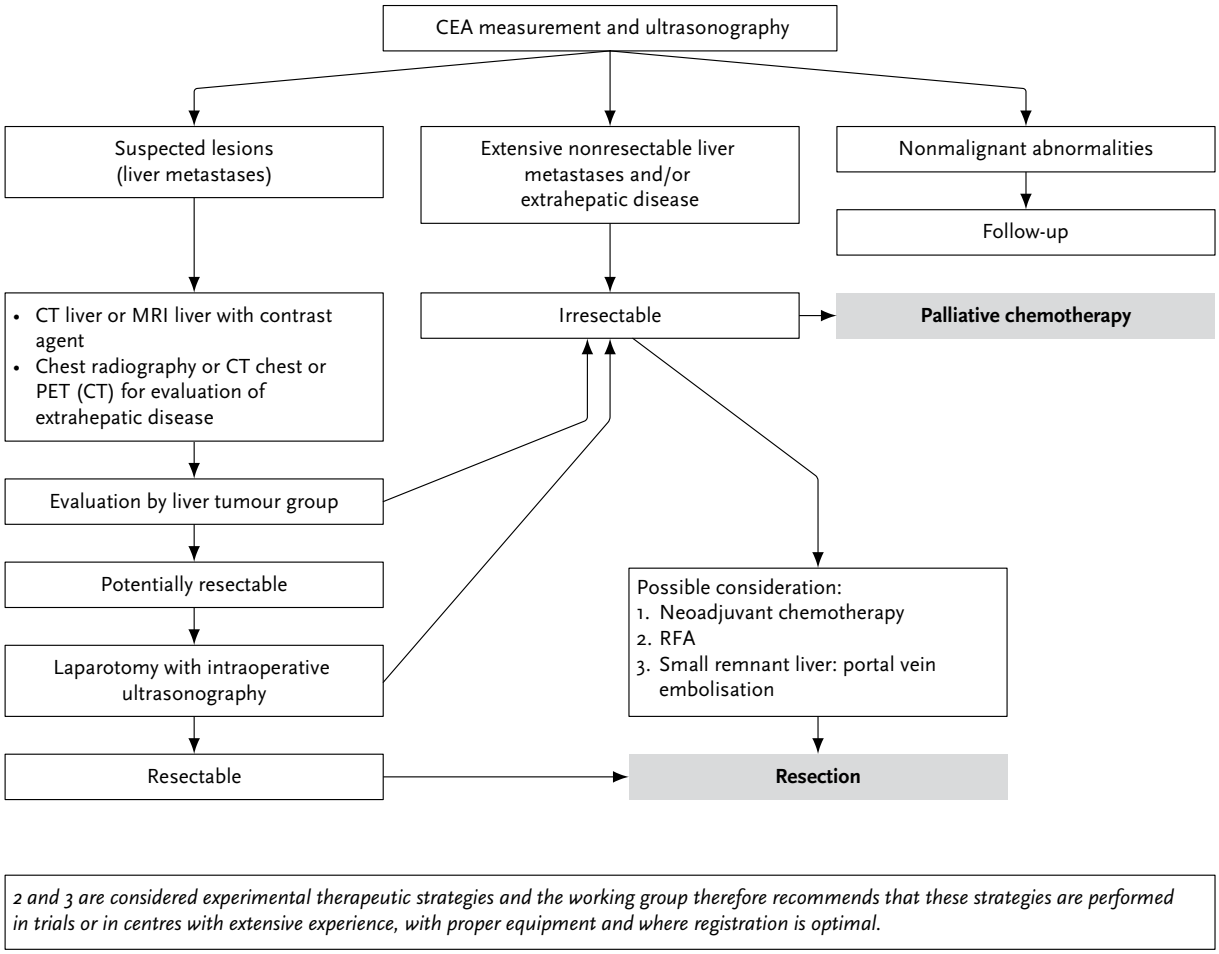
## FOLLOW-UP AFTER TREATMENT OF COLORECTAL LIVER METASTASES

When possible, surgical resection is the treatment of choice for hepatic colorectal metastases, with five-year survival rates of up to 30 to 40%. However, in most of the reported series, disease recurs in up to 80% of patients after hepatectomy. The recurrence usually involves the liver and is confined to the liver in approximately half of these cases. As with initial hepatectomy, the feasibility of repeat resection depends not only on the disease being confined to the liver but also on the distribution of hepatic disease permitting curative resection. Overall, only 23 to 33% of hepatic recurrences are resectable.[59] Repeat hepatectomy is associated with five-year survival rates equivalent to those reported for first hepatectomy[53] and therefore detecting hepatic recurrence at a resectable stage would significantly improve prognosis for this selected group of patients. The aim of follow-up, therefore, is to select patients who are candidates for repeat resection. This has also been shown in a recently published review.[56] However, there is no evidence available on the timing, frequency and the programme of follow-up. Based on the results of the studies included in the review, a follow-up visit every three months is recommended for two years, thereafter every six months until five years. Each visit is accompanied by clinical examination, CEA measurements, and CT of the chest and abdomen.

## REGISTRATION SYSTEM

Based on the survey/recommendations from the field, the working group also advocates the development of a national registration system for the diagnosis and treatment of

**Figure 1.** *Diagnostic and therapeutic strategy in the follow-up after primary colorectal tumour management*




patients with colorectal liver metastases. Registration systems are important tools in evaluating patient management. The collaboration between medical specialists and consulting specialists of the Association of Comprehensive Cancer Centres provides the possibility of a national registration.

## IMPLEMENTATION OF THE GUIDELINES

For all practitioners involved in the management of patients with colorectal liver metastases in the Netherlands, the guideline is available on www.oncoline.nl or www.vikc.nl. Although we are aware that passive dissemination of a guideline may be unlikely to lead to change, whereas the combination of several active meetings is more likely to lead to success, we firstly choose to disseminate the guideline by internet. This is because in general, guidelines for oncological diseases reported by these sites are easily implemented in daily practice. In addition, a compact and transparent summary of the guideline has been written which will be sent to all the chairmen of oncology committees in each hospital, in which referral is made to the complete guideline. Also, the working group has presented this guideline during meetings of the several disciplines involved in the management of patients with colorectal liver metastases.

There is ongoing research both on diagnosis (POLEM study) and treatment (CLOCC trial and experimental IHP, PVE). The results of these studies will most likely change the management of this patient group. Therefore this guideline should be updated, when the results of these and other relevant studies will be available.

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## APPENDIX 1

**The working group**

Chairman: J. Stoker, MD, PhD, radiologist, Academic Medical Centre, Amsterdam
Vice-chairman: J.W. Greve MD, PhD, surgeon, Maastricht University Hospital, Maastricht
Other members in alphabetic order:
S. Bipat MSc, researcher, Academic Medical Centre, Amsterdam
P.M.M. Bossuyt PhD, clinical epidemiologist, Academic Medical Centre, Amsterdam
A. Cats MD, PhD, gastroenterologist, Netherlands Cancer Institute, Amsterdam
E.F.I. Comans MD, PhD, nuclear medicine specialist, VU University Medical Centre, Amsterdam
T.M. van Gulik MD, PhD, surgeon, Academic Medical Centre, Amsterdam
R.L.H. Jansen MD, PhD, medical oncologist, Maastricht University Hospital, Maastricht
M.S. van Leeuwen MD, PhD, radiologist, University Medical Centre Utrecht, Utrecht
M.E.J. Pijl MD, PhD, radiologist, Martini Hospital, Groningen
A.S.Th. Planting MD, PhD, medical oncologist, Erasmus Medical Centre, Rotterdam,
R.A. Tollenaar MD, PhD, surgeon, Leiden University Medical Centre, Leiden
J.N.M. IJzermans MD, PhD, surgeon, Erasmus Medical Centre, Rotterdam

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REVIEW ARTICLE

# Clinical indicators: development and applications

**H. Wollersheim[1*], R. Hermens[1], M. Hulscher[1], J. Braspenning[1], M. Ouwens[1], J. Schouten[2], H. Marres[3], R. Dijkstra[1], R. Grol[1]**

[1]Centre for Quality of Care Research (WOK 117), [2]Department of General Internal Medicine; [3]Ear, Nose and Throat Department, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands, [*]corresponding author: tel.: +31 (024)-361 88 19, fax: +31 (0)24-354 17 34

## ABSTRACT

**Clinical indicators give an indication of the quality of the patient care delivered. They must comply with high-quality standards and should be constructed in a careful and transparent manner. Indicators must be relevant to the important aspects of quality of care. There should be adequate research evidence that the recommendations from which they are derived are related to clinical effectiveness, safety and efficiency. They should measure the quality in a valid and reliable manner with little inter- and intra-observer variability so that they are suitable for comparisons between professionals, practices, and institutions. Indicators are selected from research data with consideration for optimal patient care (preferably an evidence-based guideline), supplemented by expert opinion. In the selection procedure, the feasibility, such as their measurability and improvability, is important beside validity and reliability. A clinical indicator should be defined exactly and expressed as a quotient. After a try-out, the measurements and reporting should follow. The report contains an in-depth analysis of causal and contributing factors associated with the measured results. A description of the clinical circumstances and a correction for case mix should be included to allow for a justified interpretation. The indicators must be part of an improvement strategy, for which comparison feedback is often used. We give examples of indicator development and applications in oncology, diabetes care, and the use of antibiotics for treating pneumonia. We explain how comparison with reference data can be used to construct improvement programmes.**

## KEYWORDS

Clinical indicators, quality improvement, implementation, guidelines.

## INTRODUCTION

There is a sense of discomfort among doctors about the increased legislation and control in Dutch health care. Reports and articles concerning suboptimal and unsafe care are making a stronger and stronger call for accounting for the quality of care.[1] A method of public justification, introduced by the Dutch Inspectorate of Health (IGZ) and others, includes the performance indicators for hospitals. At the end of 2003, the inspectorate (www.igz.nl) presented a set of indicators[2] to the Council of Dutch Hospitals for annual publication on their web site and in their annual report.

Methods to justify the level of care activities by quantification were first used two decades ago in the United States, followed by the United Kingdom and Denmark. It is striking that care providers in Dutch hospitals are on the sidelines when it comes to the development and application of indicators. We reply in this article by describing how professionals themselves can work together in devising indicators for the quality of their activities and how they can use these indicators for the purpose of improving the quality of care.

Insight into the quality of care is necessary because research shows time and again that the quality of patient care is not optimal in 30 to 40% of the cases.[3] To acquire insight into the quality of the care provided, one can take measurements with the 'indicators'. An indicator is a measurable aspect of care provided for which there is evidence that it represents quality on the grounds of scientific research or consensus among experts.[4] There are indicators that are more suitable for internal quality improvement (clinical indicators) and indicators that are especially appropriate for external appraisal (performance indicators).[5]

From the viewpoint of measurement, there are three types of indicators: outcome, process, and structure indicators.[6] This article focuses on the clinical indicators. These are mainly process indicators, aimed at measuring and improving clinical activities in practices and care institutions.

The first part of this article describes a carefully founded systematic procedure to achieve qualitatively good clinical indicators. We have considerable experience with this procedure.[7] Compared with other methods in the literature,[8] this approach offers an acceptable balance between robustness and feasibility. The second part of this article shows, with examples, how carefully developed clinical indicators can provide insight into the quality of patient care and can support and direct improvement activities.

## METHOD OF DEVELOPMENT

It is important that clinical indicators meet careful quality requirements such as relevance, validity, reliability, and applicability.[9]

*Table 1* summarises the most important quality requirements. The clinical relevance is stipulated by the degree of scientific proof that the indicator contributes to health benefit. The indicator must represent important dimensions of care (professional care, but also organisational and patient-specific care). Clinimetrical analyses are necessary to determine the validity and reliability. Besides clinimetric properties such as face, content and construct validity also its validity in the context of its actual use should be considered. The practical usability is determined by the acceptance, measurability, and improvability. Generally, the measurability from routine value files cannot be well estimated beforehand and can best be determined by a test measurement. The result of the measurement must be useful for quality improvement. This requires that the indicator is sensitive to change, has sufficient discriminating capacity for comparison, and is useful as a decision tool.

**Table 1.** *Quality characteristics of the indicators*

| | |
|---|---|
| Relevancy | Relevant to important aspects (effectiveness, safety, and efficiency) and dimensions (professional, organisational, and patient oriented) of quality of care |
| Validity | - Strong correlation with the current quality of care<br>- Valid on the basis of good scientific proof and experience |
| Reliability | - Low inter- and intra-observer variation<br>- Available and reliable date sources<br>- Statistically reliable, i.e. reported as an average or median with confidence intervals and valid for comparison, i.e. corrected for case mix and sociodemographic variables |
| Feasibility | - Easily available<br>- Applicable to quality improvement; i.e. easy to build in improvement initiatives<br>- Sensitive to improvement in time<br>- Useful to base decisions on (caregivers, patients, regulating agencies)<br>- Applying to those who should use them |

We can take clinical indicators from the existing literature or develop them ourselves. If we use data about optimal care (from scientific research such as systematic reviews, meta-analyses or from evidence-based guidelines) in the development process, they can be augmented with experts' clinical experience in a structured consensus procedure.[10] These experts select and prioritise the recommendations. The steps for the development and practical application of indicators (*table 2*) are as follows.

**Table 2.** *Steps in the development and application of clinical indicators*

**I. Selection of relevant patient group or care process.**
Criteria:
1. Experience with care problems (variation, suboptimal care, lack of safety, complaints, costs, long waiting and process times)
2. Important to the purpose of the department, care institution, or scientific association; or of political or moral importance
3. High volume
4. Enough evidence available

**II. Literature search for indicators already developed or data about optimal care available (preferably recent evidence-based guidelines)**

**III. Composition of a balanced consensus group and application of a structured development procedure**
1. Specification. Extraction of concrete recommendations from evidence-based guidelines
2. Prioritising. Selection by an expert panel on the basis of relevance for health benefit, efficiency, measurability, and improvability

**IV. Operationalisation. Processing to definition and proportion**

**V. Availability**
1. Data. Choice of database and unambiguous method of data collection by well-instructed data collectors
2. Practice test. Test of measurability and intra- and inter-reviewer reliability

**VI. Report**
1. Statistics, tabulations, and data presentation
2. Correction for case mix and sociodemographic variables
3. Clear explanations of the results

**VII. Application to the system of quality improvement**
1. Feedback with self, external, or standard comparisons
2. Analysis and discussion of clinical indicators with a low score
3. Analysis of obstructing and conducive factors for providing optimal care
4. Formulation of improvement and implementation strategy and carrying out of the project plan
5. Monitoring of indicators as measurements of effect and for maintenance of improvement
6. Process analysis (was the improvement process carried out as agreed?)

## THE SELECTION OF RELEVANT CARE PROCESSES

First, a choice must be made about which relevant care process one wants to develop indicators for. The most

important selection criterion is the problems experienced in providing optimal care. Problems are visible if there is an unexplained variation in the care between care providers or care institutions,[11] or if it appears that data about optimum care are not applied, or not applied correctly,[12] e.g. there is consequently a lack of safety (high morbidity, mortality, complications, or errors), dissatisfaction (complaints and dissatisfaction of patients and employees), or inefficiency (capacity problems and high costs). Because developing and measuring indicators is time consuming, it is judicious to select care processes with a considerable volume (many patients and high costs of staff and resources).

## LOOKING FOR SCIENTIFIC PROOF IN THE LITERATURE

To find out whether indicators for the selected care processes have already been developed, it is advisable first to consult databases and sources of international indicators such as http://www.rand.org, http://www.ahcpr.gov, http://www.newcastle.ac.uk/qip and http://nprdc.man.uk. Indicators developed elsewhere should be tested with the criteria of relevance, validity, and reliability. They must also be adjusted to the Dutch situation to be able to give answers to the local problems. Apart from a gain in efficiency, the fact that reference values are known is an advantage when indicators are adopted. However, it is often necessary to adjust them[13] and the involvement required in developing them oneself is missing when indicators are adopted.

In order to develop clinical indicators, there must be a basis of recommendations with adequate scientific proof of their effectiveness, safety, and efficiency. A systematic search of the literature for the provision of optimal care is needed. Here we assume that evidence-based guidelines, such as those of the Dutch College of General Practitioners (NHG) and the Dutch Institute for Healthcare Improvement (CBO), act as ideal extraction sources.[14]

## THE CONSENSUS: GROUP COMPOSITION AND PROCEDURE

On the one hand, a group of experts is composed to prioritise the scientific data and on the other hand to complete the data with the knowledge of experience. National experts from a guideline committee are a logical choice. It is a good idea to augment this group of 'content experts' with some methodological experts. All the professions involved in the care process should be represented. To prevent the perspective from being limited, special attention must be paid to the participation of paramedics and specialised nurses. Besides them, managers, health economists, and patients are frequently lacking in such teams.[15] A review of studies that compared consensus methodologies shows that, starting with 12 participants, adding more participants seldom changes the result of the selection procedure in any important way.[16]

In the structured development procedure, the phases of specification and prioritisation can be distinguished:

**Specification:** At least two content experts select the core recommendations from an evidence-based guideline. Because many quality documents have a narrative design, the pretreaters must sometimes transform the consensus text into concrete recommendations.

**Prioritisation:** The second phase consists of systematic prioritising on the basis of a number of relevance requirements[8] such as the degree of evidence on which the indicator recommendation has been based[14] and the importance of the indicator for the outcome of patient care (effectiveness, safety, and costs).

The opinion of the experts can be obtained in discussions at meetings or from anonymous mail surveys. The latter is more efficient and reaches further, but it lacks the nuance of discussion and argumentation. Generally, we combine both in what is known as the Rand-modified Delphi methodology.[17] A panel of experts anonymously rates the core recommendations in writing on a point scale, for example, from 1 to 9. 'Relevance for health benefit and efficiency, measurability, and improvability' are much-used dimensions for assessing the items. The panel can make observations concerning the formulations chosen and add new recommendations. After calculating the average score of all the experts, each recommendation is accepted according to a previously determined weighting (e.g. average score above 60%), considered again, or rejected. The summarised results are discussed in the group. In a second round, all doubtful recommendations, all newly added recommendations, and all reformulated recommendations are rated again. This eventually produces a list with prioritised recommendations against which actual practice can be reviewed.

The result must balance the types (structure, process, and outcome) and the quantity of indicators well. Generally, there is some conflict between the many indicators selected (to get to the greatest possible insight into the care process), and the quantity of work which must be spent on recording. If one puts too much emphasis on minimising the recording efforts, and only a few indicators are selected, then only limited components of the care process can be judged. This can lead to neglect of important parameters that are not rated. Our experience prompts us to recommend selecting about 12 clinical indicators for a care process to achieve a good balance.

## OPERATIONALISATION

The experts operationalise the prioritised recommendations proportionally with exact descriptions of the nominator and denominator. The indicator is so defined that the larger the proportion, the better the care. The denominator describes the patient group in absolute numbers: for example for those with diabetes mellitus. The numerator reflects the actual result in the patient group. Thus, one reaches, for example, the process indicator of 'the percentage of patients for whom the $HbA_{1c}$ concentrations have been determined once a year' as a measure of the care provided for diabetes. The relevant outcome indicator here would be the percentage of diabetes patients with $HbA_{1c}$ below 7%.

## PRACTICAL TESTING

The measurements must produce reliable clinical indicators. Reliability means that there is little variation between data collectors and that the individual data collector is consistent. This requires rigid definitions and a consistent, complete, and swift manner of recording from reliable data sources. Data collectors must be trained with an eye to univocal interpretation, collection, and classification of data.

The data should preferably be collected in an automated fashion from existing files because this requires the least extra effort. Unfortunately these files often serve a purpose (e.g. financial registrations) other than indicator collection so that the definition and description of the indicator is often not exactly the same.[18]

Surveys of patients and caregivers or data from medical records serve as alternative data sources. In the case of record analysis, the subjective interpretation of notes, missing data, and the lack of considerations for making decisions reduce the reliability. The prospective collection of data to be interpreted unambiguously is, of course, the best approach, but in practical terms this often cannot be realised.

The clearer the definition and the more complete and more useful the source material is for measurement, the more reliable the results will be. Because the measurability is frequently difficult to estimate in advance and often proves to be disappointing in practice, it is wise to perform a limited test measurement beforehand. Sometimes it appears that more than half of the suggested indicators cannot reliably be measured.[19] Furthermore, test measurements often lead to refining the definitions.

## REPORTING

After further selection and adjustment on the basis of the practical testing, the collection of the definite dataset, statistical processing (reproduction in averages or medians, with the standard deviation and the confidence intervals) and reporting and interpreting of the data follows. Then tables or figures can be reproduced. The reporting often requires corrections for confounding factors such as case mix and sociodemographic variables.[20]

When data are used for comparisons there is always much discussion concerning which risk factors are important, which ones influence the results, and which risk correction method is the most suitable. To correct for confounders patient groups are often taken from similar settings, and subpopulations are excluded from the denominator or categorised in low- and high-risk populations with separate scores. A more refined methodology consists of correction on the basis of co-variables in a multiple logistic regression model.[21] A disadvantage of a sophisticated correction method is that the resulting data are difficult to understand, even for experts.

The comparison between the results obtained and reference data must challenge professionals to make improvements. There are three forms of comparison: self, external, and standard. In the relative sense, one can make comparisons with one's own performances at the time (self-comparison) or with others (external comparison, such as with best practice). In the absolute sense, one can make a comparison to a predetermined standard (benchmark). An advantage of self-comparison is that no correction for confounders is necessary, assuming that the population and patient characteristics remain rather constant in time.

## BUILDING IN A SYSTEM OF QUALITY IMPROVEMENT

Registration of the clinical indicators is not a purpose in itself; it is the base for developing and evaluating improvement strategies. The improvement interventions themselves generally consist of two steps. First, the scores are reported to the care providers; this is the feedback. The literature shows that feedback is an effective improvement strategy that, on average, leads to an improvement of 10 to 15%.[22] Second, unsatisfactory scores must trigger quality improvement.

## IMPROVEMENT PROJECTS

The impact of feedback can be maximised by having experts link it to a well-founded form of quality improvement such as periodic audits. Of course, other strategies for improvement can also be used; for a complete overview of possible improvement and implementation strategies, see www.qualitytools.ahrq.gov/qualityreport and Grol and Wensing.[23]

Within the framework of local quality improvement, the indicator is used to identify bottlenecks. If a score is unsatisfactory, an in-depth analysis must take place: why is the care the way it has been observed to be? The problems within a care process with a poor score can be inventoried, e.g. by means of surveys in which possible and feasible solutions are asked about. An analysis of obstructing and conducive factors for optimum care is essential.[24] The improvement programme is converted into a concrete project proposal with a responsible project leader. A project goal with the intended gain in the indicator score in a given time is formulated. One must take into account factors such as the investment necessary and the expected participation of those involved, and integration with initiatives already planned. It is wise to systematically review the literature regarding the planned improvement efforts. Preferably, effective elements of intervention programmes, important to the relevant problems, should be incorporated into the improvement plan. For example, we first searched the literature to detect effective elements in improving care for the chronically ill before intervention activities were executed.[25]

The project proposal contains a description of the strategy of change, taking into account the obstructing and conducive factors. Both a process analysis (was the project carried out as agreed?) and an outcome analysis (did the indicator improve as intended?) should be included. Naturally it is important to monitor the improvement in the indicator score periodically after the project so that the impact does not fade away in time.

## EXAMPLES OF DEVELOPMENT AND APPLICATION OF CLINICAL INDICATORS

Here we discuss the practical development of some clinical indicators and the results of attempts to improve the patient care. In the first example, the emphasis is on the development of clinical indicators for oncology, i.e. patients with a head or neck tumour. In the second and third examples, the emphasis is on the practice tests, the resulting scores, and the improvement strategies that are based on them. In the second example we also discuss a chronic syndrome (diabetes mellitus) with an intervention specific to the patient and in the third example to prescribing medicines (antibiotic use for pneumonia) with an intervention specific to the caregiver.

### 1. Clinical indicators for head-neck tumours

Approximately 440 new patients with malignant head or neck tumours are seen in the Radboud University Nijmegen Medical Centre every year. Problems with the coordination of care and long waiting times for treatment were the reason to start improvement activities. The availability of recent evidence-based guidelines for treating carcinomas of the larynx, the cavity of the mouth, and the oropharynx[26,27] and an active, multiprofessional, tumour working group for improvement activities satisfied a number of preconditions for a good start.

Three reviewers extracted 30 concrete recommendations from the text of the guidelines which contained 85 recommendations. There was a high degree of scientific proof that the 30 recommendations represented good care. These were presented to the members of the tumour working group in a written round. To ensure a broad perspective, the tumour working party, which consisted mainly of clinicians (nose, ear and throat doctors, mouth and jaw surgeons, radiotherapists, a medical oncologist, a radiologist, a nuclear therapist, and a pathologist), was augmented with paramedics (a logopaedist and a dietician) and a specialised nurse. In the written round, the 15 experts were asked to rate the recommendations on a scale of 1 to 9. The criterion for the score was the expected relevance for health benefit when the recommendation was put into practice. They were also asked to prioritise the recommendations (in the form of a top five), to refine the formulation, and to add any new recommendations they wished. The criteria for judging the recommendation were set beforehand as cancel (score: 1–3), doubtful (score: 4–6) and definitely include (score: 7–9 or appearing more than once in the top five priorities).[28]

In addition to the 14 clinical indicators obtained from the guidelines, four additional recommendations for good organisation of care were formulated from the literature.[25] These recommendations were connected with the fields of coordination and continuity of care. A random sample of 30 patients were also asked to rate the recommendations the same way as the professionals did. This resulted in five more indicators, which were patient specific.

The total number of the recommendations was 23. Two were not measurable at all in the practice test. The measurability of the other 21 indicators was between 35 and 97%, with an average of 57%.[29]

On the basis of low scores for baseline measurements (*table 3*), a number of improvement projects are currently being carried out. These projects include the content and fine tuning of the information supply, the logistics of the care process (a planned clinical path) and improvement of support for the patient who is making lifestyle changes (stop smoking, reduce alcohol use, and change diet) and voice rehabilitation.

### 2. Diabetes mellitus

In a way analogous to the methodology already described in the section above, 58 internists and an expert panel developed 18 indicators (12 process indicators and 6 outcome) for good diabetes care with the aid of the CBO

**Table 3.** *Overview of scores of selected* clinical indicators (percentage of patients for whom the recommendation was carried out)*

| | Scores * |
|---|---|
| For patients with head or neck tumour ($n$ = 189)[28] | |
| 1. Provision of information (12 items) | 44 |
| 2. Psychosocial support | 21 |
| 3. Swallowing and voice rehabilitation | 20 |
| 4. Lifestyle support | |
| Alcohol consumption | 25 |
| Smoking | 30 |
| Diet | 0 |
| 5. Admission time (<24 hours) | 24 |
| 6. Time to treatment (<30 days) | 29 |
| For patients with diabetes mellitus ($n$ = 1465)[29] | |
| 1. Annual foot inspection carried out | 40 |
| 2. Exercise advice given | 29 |
| 3. Smoking pattern discussed | 27 |
| 4. Weighted annually | 12 |
| 5. Achieved an $HbA_{1c}$ of <7% | 23 |
| For patients with pneumonia ($n$ = 489)[30] | |
| 1. Antibiotic recommended by guideline is prescribed | 45 |
| 2. Sputum sample taken before start of antibiotic | 54 |
| 3. Blood sample taken before start of antibiotic | 57 |
| 4. Antibiotic stopped after 3 fever-free days | 11 |

* **Selected on the basis of a low score (ie<60%)**

guidelines. An expert panel approved these indicators. Then the indicators were measured in 13 hospitals in 1460 patients with diabetes mellitus. The medical records, questionnaires, and existing data files were used for collecting data.

The average adherence to the indicators was 64%. *Table 3* shows a number of low scores. Multilevel logistic regression analysis showed which factors were responsible for the low scores. The main factors were a lack of diabetes nurses in the practice concerned and a low educational level of the patients.[30] To involve the patients more actively in the care provided, the Dutch Diabetes Federation devised a 'diabetes passport'. In addition to informative material, the passport contained a check list in everyday terms for the activities which the care provider had to carry out according to the guideline. Thus, the patient was able to take part in obtaining insight into the activities that should be carried out according to the guideline.

**3. Use of antibiotics for pneumonia**

On the basis of national and international guidelines, indicators for antibiotic use for pneumonia contracted at home were formulated in a systematic consensus procedure similar to those in the preceding examples.[31] Four of the 20 indicators were rejected because they did not fulfil the requirements of reliability and availability during the practice tests. Then the 16 remaining indicators were measured during a six-month period in the departments of internal medicine and lung diseases in eight medium-sized hospitals in a total of 1000 patients. The data were checked to see if they had to be corrected for case mix. To describe the case mix, demographic data, comorbidity, and seriousness of the disease were registered. Indeed, it appeared that the taking of blood samples for cultures was negatively influenced by the age of the patient. Sputum samples were more frequently cultured for exacerbations of chronic obstructive pulmonary disease (COPD) caused by airway infections in patients with a low score for the forced expiratory volume in 1 second ($FeV_1$).

*Table 3* shows the relatively low scores obtained for the measurements in pneumonia treatment. Especially the culturing of blood and sputum samples and the right choice and timely administration of the preferred antibiotic scored only moderately. The lowest score was for the indicator 'percentage of patients who stopped taking antibiotics three days after they were free of fever' (11%).

There were also high scores. Switching from a broad-spectrum to a narrow-spectrum antibiotic (adapted to the culture results) or from an intravenous to an oral antibiotic was performed according to the guideline in 80% of the patients. The dose or dose frequency was correctly adjusted to the kidney function in 77% of the patients.

The large variation between hospitals was striking. There was one hospital where a sputum sample was taken for every patient, while in another hospital this was only done in 24% of the patients.

The intervention programme for improving antibiotic use was aimed at the low scores and based on the interviews about factors obstructing optimal care provision. For example, the first-choice antibiotic became available at the emergency departments. It was agreed with the nurses that standard sputum and blood samples would be taken before the first administration of antibiotics.

## DISCUSSION

This article shows a manner of development and examples of application of clinical indicators. It is intended as the beginning of a discussion about how to reach a scientifically justified development and application.

During the development process the use of criteria such as relevance, validity, reliability, measurability and applicability of the indicators is essential.

The professional group for the Department of Social Medicine at the Academic Medical Centre (AMC) in Amsterdam is currently working on a development and testing instrument named AIRE (Appraisal of Indicators through Research and Evaluation). On the basis of

20 questions, the aim, relevance, setting, involvement of interested parties, the degree of scientific proof and practical use are inventoried and rated. The instrument is not yet definite and its value in practice must be still examined.

The two most important quality requirements for the indicators are that they must be based on recommendations of the highest level of scientific proof and that the data collection is reliable.

Clinical indicators are selected from qualitatively good scientific research into optimal care. They should be developed by a panel representing the occupational groups. To guarantee a high level of scientific evidence the recommendations should be extracted from an evidence-based guideline. It is still unclear which method for the production of indicators out of guidelines is the best. The composition of the panel (number of participants, representing professions, coherence in the group, dominance of individuals), the manner of prioritising (selection criteria, opportunities for correction and additions, the scale used) and the consensus procedure (rating system, research by mail or discussion meetings) each determine the outcome to a certain degree. The reliability of the consensus procedure is moderate: between 0.51 and 0.83 when expressed as kappa value.[32] The reproducibility can be improved if a high cut-off value is used, for example, above 8 on a scale of 9.

The practice test in the three investigations presented showed that between 10 and 20% of the indicators were not measurable. It is known from measurements of clinical indicators in Dutch general practices (well equipped with ICT) that an empirical test done in advance can be very worthwhile.[33] A set of 139 selected clinical indicators was examined to see if empirical data could be extracted. The available database came from a nationally representative group of general practices, the Dutch National Information Network of General Practitioners (LINH). After the empirical test, 79 of the 139 indicators were rejected. The reasons for rejection were too little validity,[18] insufficiently reliable,[25] and unsuitable data sources.[34]

Correction of sociodemographic variables and case mix is very important for a reliable interpretation. Our study shows this for antibiotic use: correction of these factors was necessary for older patient populations and for patients with more serious syndromes.

Selected clinical indicators can also be used to publicly account to society (patients, press, and government) if they are presented with clear explanations.[20] If used for external purposes, case mix correction is especially important. There is evidence that if comparison takes place and the case mix is not corrected properly beforehand, there is a risk that (well indicated) high-risk interventions will not take place, or that high-risk patient groups such as those with multiple or complicated disease will be avoided by care providers.[34] Public reporting without coercion, with the anonymity of the individual care providers, and with the necessary distinctions can reduce the threat of unjust judgement. It may prevent data manipulation and also strategic behaviour that can influence the quality of care negatively. There are indications that if feedback is given to caregivers about indicators which they themselves have devised, these undesirable effects do not occur, or occur to a lesser degree.[34] For this reason, the effect on care improvement may be greater than that of public reporting of externally developed and imposed performance indicators.

Besides the search for proper case mix correction and the most optimal use of clinical indicators, there are still many unsolved problems which require closer investigation. Important questions are:

1) What is the optimal and most unambiguous method of development?
2) How can patients and managers best be involved in development so that patient orientation and the organisation of care can also be measured?
3) How to transform the results of measuring clinical indicators into effective and efficient improvement strategies?

In this article, we contribute to this discussion.

## CONCLUSION

The development and use of clinical indicators are important steps on the way to optimising patient care. To continue on this route successfully, in the near future, investment must be made in studies to further improve the development of clinical indicators and to maximise their application. In the long run, it is desirable to link these indicators to a form of practice accreditation and a reward system. This is a course towards integration of clinical indicators into quality improvement systems that should be followed.

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ORIGINAL ARTICLE

# Inferior results with basic immunosuppression with sirolimus in kidney transplantation

**J.M. van den Akker[1*], R.J. Hené[2], A.J. Hoitsma[1]**

[1]Department of Internal Medicine, Division of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, [2]Department of Internal Medicine, Division of Nephrology, University Hospital Utrecht, Utrecht, the Netherlands, *corresponding author: tel.: +31 (0)24-361 43 64, fax: +31 (0)24-354 00 22, e-mail: a.hoitsma@NIER.umcn.nl

## ABSTRACT

**Background: The introduction of sirolimus has provided the opportunity to develop an immunosuppressive regimen without the nephrotoxic calcineurin inhibitors.**

**Methods: We conducted a first trial in 30 renal allograft recipients. Ten patients were followed prospectively and received sirolimus, to achieve a target blood level of 10 to 15 ng/ml, induction therapy with one dose of daclizumab, low-dose steroids and mycophenolate mofetil. We compared this group with a historical control group of 20 patients who received our standard treatment consisting of tacrolimus, low-dose steroids, and mycophenolate mofetil.**

**Results: After a mean follow-up of 15 weeks, seven patients developed an acute rejection in the sirolimus group (70%) compared with three patients in the tacrolimus group (15%) ($p<0.01$).**

**Because of this unacceptable high rate of acute rejections we conducted a second prospective pilot study in nine patients. These patients received sirolimus in combination with two doses of daclizumab, high-dose steroids and mycophenolate mofetil. No rejections occurred under this immunosuppressive regimen; however, many immunosuppression-related adverse events were seen.**

**Conclusion: The present study demonstrates an unacceptably high rate of acute rejections (70%) in patients treated with sirolimus, daclizumab, mycophenolate mofetil and low-dose prednisolone. No rejections but many adverse events were seen when sirolimus was given in combination with high-dose steroids.**

## KEYWORDS

Calcineurin inhibitor, kidney transplantation, rejection, sirolimus, adverse events

## INTRODUCTION

Immunosuppressive regimens including calcineurin inhibitors have greatly improved the results of kidney transplantations. Tacrolimus in combination with mycophenolate mofetil (MMF) and prednisolone decreased the number of acute rejection episodes within the first three months after transplantation to 15 to 20%. The incidence of graft failure from intractable acute rejections within one year after transplantation has dropped under the current regimen to below 5%. Therefore, tacrolimus combined with MMF and prednisolone is the standard regime in the first four months after transplantation in our centres. However, calcineurin inhibitors are nephrotoxic, which may eventually lead to loss of graft function. Long-term results are therefore disappointing. The introduction of sirolimus has provided the opportunity to develop an immunosuppressive regimen without nephrotoxic calcineurin inhibitors.[1]

Obviously, removing calcineurin inhibitors from the immunosuppressive regime should not lead to a higher percentage of rejections. On the other hand, the additional amount of immunosuppression needed beside sirolimus to prevent acute rejection should not lead to an unacceptable amount of immunosuppression-related adverse events. Recently, Flechner *et al.*[2] demonstrated in kidney transplant recipients that treatment with sirolimus, prednisolone, MMF, and additional IL-2 receptor blocker (basiliximab) was accompanied with an acute rejection percentage of 6.4%. However, the additional immunosuppression given, high-doses of steroids and two induction therapies, is much more than we are used to giving in combination with tacrolimus.

The main purpose of our study was to investigate whether the nephrotoxicity that occurs under the current standard immunosuppressive regimen with tacrolimus, low-dose

steroids and MMF can be decreased by a regimen with sirolimus, daclizumab, low-dose steroids and MMF without an increased incidence of acute rejections.

## MATERIALS AND METHODS

### Patients

We included primary and secondary adult (aged above 18 years) renal allograft recipients in Nijmegen and Utrecht. Exclusion criteria consisted of HLA-identical living donor kidney; haemolytic uraemic syndrome as original renal disease; pregnancy or lactation; total white blood cell count $<3*10^9$/l or platelet count $<100*10^9$/l or haemoglobin level <5 mmol/l; current panel reactive antibodies (PRA) (last screening sample) >85%; the use of non-registered medication during the last four weeks preceding transplantation and during the study, a renal allograft transplant as part of a multiorgan transplantation; or treatment with CYP3A4 inhibitors or inductors. All recipients had a negative visual complement dependent cytotoxicity crossmatch. Flow cytometry T-cell crossmatching did not take place.

The patients who gave their informed consent were prospectively followed and treated with a calcineurin inhibitor free immunosuppressive protocol including sirolimus, daclizumab, MMF and low-dose steroids. This group was compared with a historical control group consisting of patients who met the same inclusion and exclusion criteria and had been treated directly before the start of the study with our standard immunosuppressive regimen including the calcineurin inhibitor tacrolimus, MMF and low-dose steroids.

The study was approved by both ethical committees of the participating centres and performed in accordance with the standards of the Declaration of Helsinki.

### Immunosuppressive protocol and methods

*First study*

The patients in the calcineurin inhibitor free intervention group were treated with sirolimus at a loading dose of 15 mg prior to transplant surgery. As soon as a patient was capable of taking oral medication a second loading dose of 12 mg was given, followed by a daily dose of 6 mg, to achieve a target blood level of 10 to 15 ng/ml. The target trough level remained steady throughout the study.

The patients in the sirolimus treatment arm also received daclizumab during the transplant surgery intravenously at a dose of 1 mg/kg. At weekly intervals during the first ten weeks following transplantation, the coverage of IL-2 receptors was measured by flow cytometry.[3] If free IL-2 receptors were detected on the lymphocytes (reappearance of $CD3^{pos}CD25^{pos}$ lymphocytes) in the first four weeks, an extra dose of daclizumab at 1 mg/kg was given.

The steroid regimen in the sirolimus treatment arm consisted of 100 mg prednisolone intravenously on day 0 (day of transplantation); on day 1 to 5 prednisolone 4 times 25 mg orally/iv. From day 6 till week 17 the steroids were slowly reduced from the starting dose (determined by weight: >70 kg: 25 mg; 50 to 70 kg: 20 mg; <50 kg: 15 mg) to zero.

Patients in the historical control group were treated with tacrolimus at a dose of 0.2 mg/kg/day orally, divided over the morning and evening doses, to be started on day 1 or 2 after transplantation. The target blood level in the first 14 days was between 15 and 20 ng/ml, from week 3 to 7 between 10 and 15 ng/ml and starting from week 7 the trough level should be 6 to 10 ng/ml.

The steroid regimen in the tacrolimus treatment group consisted of 100 mg prednisolone intravenously on day 0 (day of transplantation); on day 1 and 2 prednisolone 25 mg four times orally/iv. From day 3 till week 17 the steroids were slowly reduced from the starting dose (determined by weight: >70 kg: 25 mg; 50 to 70 kg: 20 mg; <50 kg: 15 mg) to 0.1 mg/kg.

All patients were given MMF 750 mg twice daily from day 1 or 2 onwards. For patients with a body weight of ≥90 kg, the dose was 1000 mg twice daily. In case of leucopenia or abdominal complaints, the dose was lowered (the minimal dose is 250 mg twice daily).

All patients in whom a rejection was suspected underwent renal transplant biopsy, which were scored according the BANFF97 criteria.[4] The primary study endpoints were the difference in renal function and the number of acute rejections between both treatment groups.

*Second study*

Because of the unacceptably high rate of acute rejections in the above-described patients treated with sirolimus (see results) we conducted a second prospective pilot study in nine patients. They received sirolimus and MMF following the same protocol as described above. Besides the daclizumab given during the transplant surgery, they received an additional dose of daclizumab 1 mg/kg ten days after transplantation. The steroid regimen consisted of 500 mg methylprednisolone intravenously on day 0 (day of trans-plantation) to 2, and then oral prednisolone from 120 mg to 30 mg by day 8, 27.5 mg by day 21, 25 mg by day 30, tapered by 2.5 mg each month to a maintenance of 7.5 mg daily.

### Results

*First study*

Ten patients included in the sirolimus group were compared with 20 patients who were treated with tacrolimus. Patient characteristics are summarised in *table 1*. Apart from more older donors and an unfavourable donor type profile in the sirolimus group, no significant differences were found. After a mean follow-up of 15 weeks, seven patients

in the sirolimus group had developed an acute rejection (70%; 95% confidence interval 42 to 98%). This was significantly more than the 15% rejection rate in the control group ($p<0.01$; Fisher's exact test). Characteristics of the rejection episodes that occurred in the sirolimus group are mentioned in *table 2*. In four patients the renal allograft function recovered after three pulses of solumedrol alone. Two patients required a second course of solumedrol and one patient required antithymocyte globulin (ATG) after the solumedrol treatment before renal function improved. All patients were converted to tacrolimus and returned to a stable allograft function, with a mean serum creatinine of 159 μmol/l at one year after transplantation.

Four rejection episodes occurred within two weeks after transplantation. One of them was not biopsy proven because of the absence of renal tissue in the biopsy. In one of these patients there appeared to be no IL-2 receptor blockade because the patient did not receive any daclizumab by mistake. In all the patients who received daclizumab, the IL-2 receptor was fully blocked at two and three months after transplantation after one dose of daclizumab.

Three rejections occurred between 8 and 15 weeks after transplantation. In all these cases the trough sirolimus level appeared to be below the target range at the time of rejection. The mean sirolimus trough levels were within the target range in the different time periods (*table 3*), but 21% of the measurements were below target. This was comparable with 19% of the measurements below target in the tacrolimus treatment group.

**Table 1.** *Demographics of the first study*

| | Sirolimus (n=10) | Tacrolimus (n=20) | P |
|---|---|---|---|
| **Recipients** | | | |
| Gender (M:F) | 7:3 | 10:10 | NS |
| Age (years) (mean ± sd) | 54 ± 14 | 46 ± 13 | NS |
| Age >65 years | 3 | 1 | NS |
| **Donors** | | | |
| Gender (M:F) | 2:8 | 8:12 | NS |
| Age (years) mean ± sd) | 52 ± 15 | 47 ± 12 | NS |
| Age >65 years | 3 | 0 | 0.03 |
| **Secondary transplant** | 1 | 1 | NS |
| **PRA** =0% | 10 | 18 | NS |
| >0 and <50% | 0 | 2 | |
| **HLA mismatches** (mean ± sd | 2.8 ± 0.9 | 2.5 ± 1.5 | NS |
| **Donor type** | | | |
| Low risk (HB+LR) | 3 | 14 | NS |
| High-risk (NHB+LUR) | 7 | 6 | P<0.05 |

**M = male; F = female; PRA = panel reactive antibodies; HLA = human leucocyte antigen; NHB = non-heart beating; HB = heart beating; LR = living related; LUR = living unrelated; NS = not significant.**

**Table 2.** *Sirolimus-treated patients with acute rejections in the first study (n=7)*

| **Rejections** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|
| Week after KTx | 2 | 1 | 14 | 15 | 8 | 2 | 1 |
| Donor type | NHB | HB | LUR | LUR | LUR | LR | LR |
| HLA mismatches (A-B-Dr) | 1-0-0 | 0-2-1 | 1-1-1 | 1-1-2 | 0-1-2 | 1-1-1 | 1-1-1 |
| Sirolimus level at rejection (ng/ml) | 12 | 11 | 7.3 | 6.8 | 7.3 | 23 | 12 |
| IL-2R blockade at 3 months | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Doses MMF at rejection (g/day) | 1500 | 1500 | 1500 | 1500 | 1500 | 1500 | 2000 |
| Steroid dose at rejection (mg/day) | 20 | 25 | 2.5 | 2.5 | 7.5 | 22.5 | 25 |
| Banff score: | | | | | | | |
| First biopsy | IIa + ATN | Ib | Ib | IIa | Ib | No renal | IIa |
| Second biopsy | IIa | | Ia | | | tissue | |
| Therapy | 3g Sol (twice) | 3g Sol | 3g Sol (twice) | 3g Sol | 3g Sol | 3g Sol ATG | 3g Sol |
| Creatinine one year after transplantation | 230 | 168 | 130 | 160 | 147 | 126 | 150 |

**KTx = kidney transplantation; NHB = non-heart beating; HB = heart beating; LUR = living unrelated; LR = living related; HLA = human leucocyte antigen; IL-2R blockade = interleukin 2 receptor blockade; MMF = mycophenolate mofetil; ATN = acute tubular necrosis; Sol = solumedrol; ATG = antithymocyte globulin.**

**Table 3.** *Sirolimus and tacrolimus trough levels in the first and second study*

| | 0-14 days | 2-7 weeks | 7 weeks-3 months |
|---|---|---|---|
| Tacrolimus trough level (ng/ml): | | | |
| Target | 15-20 | 10-15 | 5-10 |
| Actually reached (mean ± SEM) | 16.4 ± 0.9 | 12.3 ± 0.4 | 9.3 ± 0.3 |
| Sirolimus trough level (ng/ml): | | | |
| Target | 10-15 | 10-15 | 10-15 |
| Actually reached (mean ± SEM): | | | |
| - First study | 13.4 ± 1.1 | 14.9 ± 1.0 | 11.8 ± 1.0 |
| - Second study | 10.8 ± 0.8 | 15.6 ± 0.9 | 13.1 ± 0.9 |

**SEM = standard error of the mean.**

One sirolimus-treated patient had a serious wound-healing problem.

Two of the three rejections in the tacrolimus group occurred within one week after transplantation. The third rejection occurred after 11 weeks. All of the patients required ATG after the course of solumedrol. One of them died as a consequence of this therapy.

*Second study*

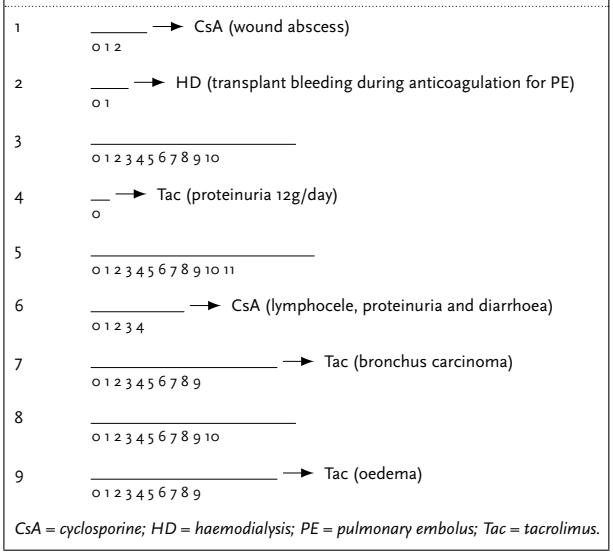
No acute rejections occurred in the second sirolimus treatment group (n=9) with high-dose additional immunosuppression after a mean follow-up of ten months. On the contrary, many serious adverse events were seen in this group, as summarised in *table 4*. Six patients (67%) suffered delayed wound healing, with a secondary wound infection in three of them. Operative abscess drainage was necessary in one of them. Four patients (44%) developed a lymphocele requiring drainage. In one patient a secondary infection developed in the lymphocele. One patient developed a pulmonary embolus and thereafter during anticoagulation therapy a bleeding in the transplant. After insertion of a vena cava filter, a vena cava inferior syndrome occurred and because of continuous bleeding in the kidney transplant a transplantectomy was performed and haemodialysis was restarted. Three patients (33%) developed proteinuria after transplantation. One of them is the above-described patient with pulmonary embolus. Another patient developed proteinuria of 12 g/day one week after transplantation. A kidney biopsy showed tubulointerstitial damage without glomerular damage. The proteinuria disappeared within one month after switching to tacrolimus. The third patient with proteinuria developed proteinuria till 1.5 g/day, which also disappeared after switching to cyclosporine. Three patients developed diarrhoea (33%), two of them requiring hospitalisation.

Three patients could be maintained on the sirolimus regimen during the mean follow-up period of ten months. The other six patients were switched to another immunosuppressive regimen because of severe complications. The time till the switch of immunosuppression and the main reason for switching is shown in *figure 1*. Two patients were switched to cyclosporine (after two and four months), three patients were switched to tacrolimus (one after one week and two after nine months), and one patient restarted haemodialysis after nephrectomy (seven weeks after transplantation).

**Table 4.** *Adverse events in sirolimus-treated patients (second study)*

| Patient no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Acute rejection | - | - | - | - | - | - | - | - | - |
| Graft loss | - | + | - | - | - | - | - | - | - |
| Surgical complications | | | | | | | | | |
| - Delayed wound healing | + | + | + | - | + | + | + | - | - |
| - Haematoma | + | - | - | - | - | - | - | - | - |
| - Wound abscess/infection | + | + | - | - | + | - | - | - | - |
| - Lymphocele | - | - | + | - | + | + | + | - | - |
| Hypercholesterolaemia (>6 mmol/l) | - | - | - | - | + | + | + | + | - |
| Hyperglycaemia (fasting glucose >7 mmol/l) | + | + | - | - | - | + | - | - | - |
| Pulmonary embolus | - | + | - | - | - | - | - | - | - |
| Proteinuria (>1g/day) | - | + | - | + | - | + | - | - | - |
| Candidiasis (oral) | + | - | - | - | - | - | - | - | - |
| Diarrhoea | - | - | + | - | + | + | - | - | - |

**Figure 1.** *Time frame (in months) for sirolimus-treated patients: reason for switch of immunosuppression (second study)*




*CsA = cyclosporine; HD = haemodialysis; PE = pulmonary embolus; Tac = tacrolimus.*

## DISCUSSION

The use of calcineurin inhibitors has resulted in improved graft survival following kidney transplantation. However, this is associated with acute and chronic nephrotoxicity and may be an important contributor to the development of chronic transplant nephropathy and chronic graft loss.[5] Calcineurin inhibitor nephrotoxicity is becoming increasingly prevalent, and is virtually universal by ten years after transplantation and progressive despite mild to moderate reductions in calcineurin doses.[6] The introduction of sirolimus has provided the opportunity to develop an immunosuppressive regimen without nephrotoxic calcineurin inhibitors. Recently, Flechner *et al.*[2] demonstrated in kidney transplant recipients that treatment with sirolimus, prednisolone, MMF and additional IL-2 receptor blocker (basiliximab) was accompanied with an acute rejection percentage of 6.4 *vs* 16.6% in the control arm (cyclosporine, prednisolone, MMF and IL-2 receptor blocker). At 12 months their sirolimus-treated patients enjoyed significantly better creatinine clearances than their cyclosporine-treated patients (81.1 and 61.1 ml/min, respectively). However, the additional amount of immunosuppression given beside sirolimus is very high.

In our first study we achieved a rejection percentage of 70% in the sirolimus group compared with a 15% rejection rate in the tacrolimus group ($p<0.01$) within a mean follow-up of 15 weeks. Because of this unacceptably high rejection rate we ended the study prematurely and switched the patients to the standard immunosuppressive regimen including tacrolimus. To date, none of the patients have lost their grafts in the mean follow-up of 18 months. This high percentage of rejections cannot be explained by the fact that only patients with a high rejection risk were included in the sirolimus group. All rejections occurred in patients who underwent a first kidney transplantation with a PRA of 0% and there were no significant differences in the number of HLA mismatches and number of non-heart beating donors between the groups. However, when we divided the donors into a low-risk group (heart beating and living related donors) and a high-risk group (non-heart beating and living unrelated donors) significantly more patients with an unfavourable donor type were found in the sirolimus-treated patients. Although this can be partly responsible for the bad outcome in the sirolimus group we do not think this can totally explain the very high rejection rate of 70%.

Four of the seven rejections in the sirolimus group occurred within two weeks after transplantation. One of these rejection episodes occurred in a patient who did not receive any daclizumab by mistake. In all other patients the IL-2 receptor was fully blocked at two and three months after transplantation by one infusion of daclizumab during transplant surgery. Three of the seven rejections occurred between 8 and 15 weeks after transplantation. These three rejections occurred when the prednisolone was reduced to below 10 mg/day, in accordance with the protocol. All patients used at least 1500 mg MMF during the study period. At the time of rejection the sirolimus levels appeared to be lower than the target level in all three of them. The sirolimus levels were below target in 21% of all measured levels in the sirolimus group, but were never measured below 6.8 ng/ml. In the tacrolimus group 19% of all measured levels were below the target level. Some fluctuation in (sirolimus) trough levels is inevitable, but we must conclude that this seems immediately catastrophic in our low immunosuppressive regimen of the sirolimus group. There have been reports of calcineurin inhibitor free therapy, even without using antibody induction, that describe lower rates of acute rejection than we found. Kreis *et al.*[7] using sirolimus, MMF and steroids reported an acute rejection rate of 27.5% one year after transplantation and Groth *et al.*[8] using sirolimus, azathioprine and steroids reported an acute rejection rate of 41% at one year. In comparison with our protocol the target trough sirolimus level amounted to 30 ng/ml for the first two months in both studies and they started with 500 mg of methylprednisolone tapered to a maintenance dose of 10 mg daily. In the Symphony trial standard immunosuppression with normal dose cyclosporine (target trough level 150 to 300 ng/ml) was compared with three regimens with low doses of either cyclosporine, tacrolimus or sirolimus in combination with MMF, daclizumab and corticosteroids in 1645 *de-novo* renal transplant patients. The rate of biopsy-proven acute rejections with low-dose sirolimus (target trough level 4

to 8 ng/ml) at one year (35%) was higher than in the other groups (15 to 25%). The conclusion of this study was that the room for increasing sirolimus immunosuppression should be evaluated against the specific sirolimus toxicity profile.[9,10] Contrary to our study, Flechner *et al.* started with 500 mg methylprednisolone intravenously on day 0 to 2, and then oral prednisolone from 120 mg to 30 mg by day 8, and thereafter slowly tapered to a maintenance dose of 7.5 mg daily at eight months. Their mean trough sirolimus levels appeared to be 13.2 ± 7.9 ng/ml at one month after transplantation and 11.2 ± 5.8 ng/ml at three months after transplantation. They also gave a higher dose of MMF of 1 g twice daily instead of the 750 mg twice daily in our study and they used two gifts of basiliximab. These differences might explain the high rejection rate we found.

To prove this supposition we conducted a second prospective trial in nine patients. This protocol differed from the first by an additional dosage of daclizumab 1 mg/kg at ten days after transplantation and higher doses of MMF and steroids according to the Flechner protocol. No acute rejections occurred under this treatment regimen. On the contrary many serious adverse events were seen, likely to be related to the combination of sirolimus and high-dose steroids. These findings are in accordance with Dean *et al.*[9] using sirolimus, six gifts of antithymocyte globulin induction, MMF, and prednisone. They achieved an acute rejection rate of 9% at one year, but a wound complication rate of 35% in comparison with 10% in the tacrolimus control group. These adverse events and the interventions needed to treat them might also lead to a decline in renal function. This takes away the advantage of sirolimus, no nephrotoxicity, in the first place. However, the number of treated patients in our study is too small to compare renal function under the different regimens. In the Symphony trial where renal function was determined at 12 months they showed that low-dose tacrolimus was significantly superior to low-dose sirolimus with respect to glomerular filtration rate.[11] The results from our study showed that in order to replace a calcineurin inhibitor by sirolimus aiming to avoid calcineurin nephrotoxicity, higher additional immunosuppression is needed to prevent an unacceptable rejection rate. Because of the immunosuppression-related adverse events we experienced under such a regimen we do not think there should be a place for a sirolimus-based regimen without calcineurin inhibitor in the direct post-transplant period.

## CONCLUSION

The present study demonstrates an unacceptably high rate of acute rejections (70%) in patients treated with sirolimus, daclizumab, MMF and low-dose prednisolone in the first months after transplantation and no rejections but many adverse events when sirolimus was combined with two times induction therapy and high-dose prednisolone.

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ORIGINAL ARTICLE

# Binge drinking causes endothelial dysfunction, which is not prevented by wine polyphenols: a small trial in healthy volunteers

**M.L. Hijmering[2], D.W. de Lange[1*], A. Lorsheyd[2], R.J. Kraaijenhagen[3], A. van de Wiel[2]**

[1]Thrombosis and Haemostasis Laboratory, University Utrecht, Utrecht, the Netherlands,
[2]Department of Internal Medicine, Meander Medical Centre, Amersfoort, the Netherlands,
[3]Department of Clinical Chemistry, Meander Medical Centre, Amersfoort, the Netherlands,
[*]Corresponding author: tel.: +31 (0)30-250 30 37, e-mail: D.W.deLange@umcutrecht.nl

## ABSTRACT

**Background: Binge drinking (the consumption of large quantities (>5 units) of alcohol in a short period) is associated with increased cardiovascular mortality. Wine polyphenols are considered to be protective against cardiovascular diseases. We conducted an experimental study to evaluate the acute effects of alcohol consumption on flow-mediated vasodilation and general cardiovascular parameters, using beverages with high polyphenolic content (HPC) and low polyphenolic content (LPC).**

**Methods: Two groups of ten volunteers were asked to drink two different kinds of beverages. In 45 minutes, three units of red wine or an alcoholic beverage with a low polyphenolic count were consumed. Then 45 minutes were allowed for complete uptake of the alcohol or polyphenolic compounds. Next, all volunteers underwent blood pressure readings, ECG and flow-mediated vasodilation. Blood samples were taken at the same time for routine chemistry, inflammation parameters and lipids. Then the entire cycle was repeated once (in total six units of alcohol in 180 minutes).**

**Results: No differences were found between the two drinks. Alcohol itself dose-dependently increased forearm blood flow by vasodilation of both arterioles and distribution arteries. However, flow-mediated vasodilation (FMD) for the LPC group (n=10) decreased from 7.31 ± 4.78 (% ± SD) to 2.82 ± 2.9 after three drinks and 1.21 ± 3.25 after six drinks. The FMD values for the HPC group (n=10) decreased from 8.61 ± 1.78 to 1.78 ± 3.71 and 1.19 ± 2.6. There were no significant changes between the LPC and the HPC group at the three time points.**

**Conclusion: Although ethanol produces vasodilation at the level of the distribution artery as well as at an arteriolar level, it causes a decrease in flow-mediated vasodilation. This endothelial dysfunction is not corrected by the polyphenols present in wine.**

## KEYWORDS

Alcohol, flow-mediated vasodilation, ethanol, polyphenols, cardiovascular disease

## INTRODUCTION

The relationship between alcohol consumption and the incidence of atherosclerotic diseases has raised many debates. According to the results of large epidemiological studies, chronic moderate alcohol consumption, on average one unit a day, appears to have a protective effect on cardiovascular disease.[1] The mechanisms involved are not completely clear and various explanations have been given. In contrast to this cardioprotection, overconsumption of alcohol in a short period of time (binge drinking) results in increased cardiovascular mortality, especially sudden death, and acute coronary artery syndromes. This is of importance as the so-hailed moderate drinking pattern is not at all common. A study indicated that most light drinkers do not drink daily and most daily drinkers are not light drinkers.[2] Although the focus of most scientific articles has been on the cardioprotective effects of alcohol, the drinking pattern of our youths might actually put them at risk for cardiovascular events.

The cardioprotective effects of alcohol have been attributed to the increase in high-density lipoprotein cholesterol (HCL-c), decrease in plasma fibrinogen concentrations, or reduced platelet activity.[1] Additionally, cardioprotection may also be exerted by stimulation of endothelial nitric oxide synthase and decreased oxidative stress,[3] which may lead to an increase in nitric oxide (NO) production. NO has a central role in counteracting most processes that eventually lead to atherosclerosis. Furthermore, ethanol consumption influences the fibrinolytic system as well as the composition of serum lipids.[1] Several authors have suggested that not ethanol per se, but other constituents of alcoholic beverages are responsible for the antiatherogenic action. Especially flavonoids, a group of phenols present in red wine, are attributed antiatherogenic abilities. They are capable of scavenging reactive oxygen species. Reactive oxygen species are highly reactive chemicals that, within the scope of atherosclerosis, produce cell damage and promote the vicious circle that results in atherosclerosis. Additionally, flavonoids stimulate the production of nitric oxide. Furthermore, red wine polyphenols can limit the effects of endothelin-1 (ET-1).[4] ET-1 is one of the most powerful vasoconstrictors, produced locally by the endothelium. Levels of endothelin-1 are increased in heart failure, hypertension and other disease states that are associated with the development of atherosclerosis. Interestingly, alcohol is capable of stimulating ET-1 release by the endothelium directly.[5]

The acute effects of alcohol consumption have been investigated in previous studies. Results of these studies are conflicting because of the differences in study design and the population that is under investigation. In healthy, young volunteers the main vascular consequence of an acute dose of alcohol is vasodilatation.[6-9] However, there is no consensus on its action on FMD. Hashimoto *et al.* observed a decrease in FMD after acute alcohol use, but FMD increased after consumption of de-alcoholised red wine.[7] This suggests that the nonalcoholic constituents of red wine counteract the decrease in FMD caused by alcohol. However, others did not observe any change in endothelial function by red wine[6,10] or even an increased FMD after the acute consumption of alcohol.[11] Unfortunately, most of the studies of alcohol effects on endothelial function could be affected by confounding factors. Arterial diameter and endothelial function measurements are extremely vulnerable to variables such as diseases, medication use, atherothrombotic risk factors, gender, age, menstrual cycle, postprandial period, and temperature.[12]

In short, moderate and prolonged alcohol and red wine consumption is associated with cardioprotection and possibly improved endothelial function in patients, but still little is known about the acute effects of a binge in healthy volunteers. We hypothesised that a binge might have opposite, more deleterious effects that might explain the increased morbidity associated with this kind of drinking pattern.[13-15] We therefore designed a binge drinking trial in volunteers without cardiovascular risks to assess the acute effects of ethanol on endothelial reactivity and cardiovascular parameters, using drinks with and without a high polyphenolic content.

## MATERIALS AND METHODS

All studies were conducted in a single teaching hospital under standardised conditions, which included room temperature of 20 °C, no caffeine consumption in the week prior to the study, no eating or drinking for at least four hours before entering this study, no consumption of alcohol and no smoking one week prior to the study. To be eligible for inclusion, volunteers needed to be healthy in general terms, and were not on any medication that may have had an effect on the cardiovascular parameters measured. Other exclusion criteria included smoking within the last six months, body mass index >30 kg/m$^2$, cardiovascular diseases (assessed by clinical history taking, physical examination or ECG), diabetes mellitus, blood pressure >149/90 mmHg or treatment with antihypertensive agents, use of lipid-lowering medication or nonsteroidal anti-inflammatory drugs. None of the females who participated in this trial was using oral contraceptives, but we have no information on the phase of their menstrual cycle. Before agreeing to participate in this trial the volunteers consumed one alcoholic beverage a day on average. The local ethics committee approved the study protocol and all volunteers signed an informed consent form. This study was carried out in accordance with the Declaration of Helsinki (1998) of the World Medical Association.

All studies were performed on a single day, starting at 6 pm. A typical study day started with a further explanation of the study protocol. Next, an 18-gauge cannula was inserted in a large cubital vein of the dominant arm for blood sampling. An ECG was recorded according to standard methods followed by automated noninvasive blood pressure measurements (SureSign by Phillips Medical) and flow-mediated vasodilation examination.

### Drinks

The 20 volunteers were randomised to either the red wine group or the low-polyphenolic group. In total ten volunteers drank red wine and ten drank the low-polyphenolic Barcardi Breezer. The volunteers were asked to drink three glasses of an alcohol-containing beverage, either Barcardi Breezer (275 ml with 5.0 vol% of alcohol, adding up to 11 gram alcohol per drink) or red wine (Rioja, 110 ml with 13.0 vol% of alcohol, adding up to 11.4 gram of alcohol per glass). These drinks were chosen because red wine has a high polyphenolic count (HPC) and the Barcardi Breezer has a low polyphenolic

count (LPC) and is a popular binge drinking consumption in youths. These three drinks were consumed within a 45-minute period. After the third drink, 45 minutes were allowed for alcohol uptake into the circulation.[16] After these 90 minutes, examination of flow-mediated vasodilation was performed and blood was collected for haematological and biochemical parameters. Then this cycle was repeated and after 180 minutes flow-mediated dilatation was examined and blood was collected for a second analysis. The polyphenols in the Rioja were measured by HPLC and the highest concentrations were catechin 11 mg/l, epicatechin 5 mg/l, quercetin 1 mg/l and gallic acid 45 mg/l.

**Chemistry**

Routine chemistry consisted of blood cell count, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase (γGT), alkaline phosphatase, carboxyl deficient transferrin (CDT) and lipids. CDT and γGT levels were used to screen for chronic alcohol (ab)use, although the average alcohol consumption was one drink daily. Blood cell counts were performed on Sysmex SE-9000, Sysmex TOA, Kobe, Japan. Chemistry and ethanol levels were performed on an LX20 from BeckmanCoulter, Brea (LA), California, USA.

**Flow-mediated vasodilation**

The technique of flow-mediated vasodilation (FMD) is an elegant noninvasive technique, which tests the capability of a forearm artery to dilate in response to a flow stimulus. Inhibition of FMD is generally considered to reflect endothelium dysfunction. Numerous studies have shown that loss of vasodilation is associated with the extent of atherosclerosis in a patient. Moreover, the endothelial function measured in the forearm arteries correlates nicely with the endothelial function of the coronary artery. In our study, we used B-mode ultrasonography on an ATL HDI 5000 operating at 7.5 to 12.5 MHz with focus points on the 'near' and 'far' walls. All measurements were performed in the nondominant arm by the same investigator. These recordings were subsequently analysed off-line by an interpreter unaware of the alcohol level. This technique has been described extensively and found to be reproducible.[17]

**ECG**

All ECGs were recorded on a Siemens ambulant electrocardiography machine. All ECGs were manually interpreted, and the reader was unaware of the alcohol level of the individual.

**Statistical analysis**

All measurements took place at predefined time points (before, after three drinks and after the full dose). We used the actual serum alcohol level rather than the fixed time point in analysis. Both groups, high polyphenolic content (HPC) and low polyphenolic content (LPC), were tested for normality and differences were detected by performing repeated-measures ANOVA. In case of a non-normal distribution a Wilcoxon signed-rank test or Mann-Whitney rank-sum test was used. A level of $p<0.05$ was considered significant.

A regression analysis was performed on the effect of the delta (observed value – baseline value) FMD values in relation to the delta serum ethanol level (LPC) and delta alcohol levels in the red wine group (HPC) and curves were constructed.

## RESULTS

In total 20 volunteers completed the study. Baseline characteristics of the study population are summarised in *table 1*. None of the baseline characteristics were significantly different between the two groups.

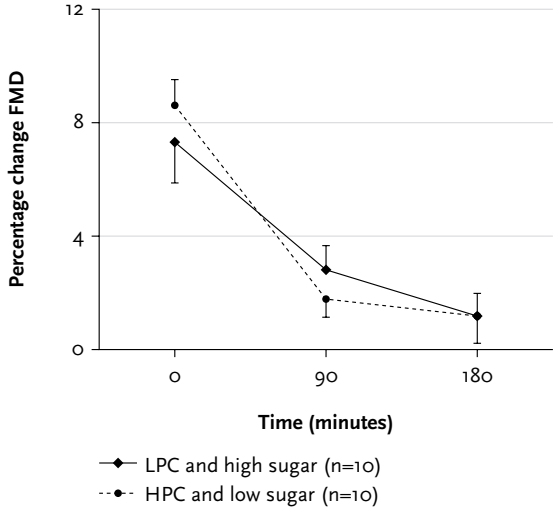
**Endothelium and nonendothelium dependent changes in local haemodynamics**

**Table 1.** *Baseline characteristics. All values are means with standard deviation in brackets*

| | LPC | HPC | P value |
|---|---|---|---|
| Gender (male/female) | 7/3 | 6/4 | NS |
| Age (years) | 34.7 (10.6) | 36.4 (9.0) | NS |
| Height (cm) | 179 (11.4) | 180.1 (6.9) | NS |
| Bodyweight (kg) | 77.5 (11.1) | 79.8 (14.0) | NS |
| Mean arterial blood pressure (mmHg) | 114.8 (12) | 111.6 (13) | NS |
| Carboxyl deficient transferrin (%) | 2.20 (0.49) | 2.58 (1.18) | NS |

Flow mediated vasodilation (FMD) for the LPC group (n=10) decreased from 7.31 ± 4.78 (% ± SD) to 2.82 ± 2.9 after three drinks and 1.21 ± 3.25 after six drinks. The FMD values for the HPC group (n=10) decreased from 8.61 ± 1.78 to 1.78 ± 3.71 and 1.19 ± 2.6. There were no significant changes between the LPC and the HPC group at the three time points. These changes in FMD have been visualised in *figure 1*. The flow through the brachial artery as measured by B-mode ultrasonography of the LPC group rose significantly from 54 ± 40 to 87 ± 41 and 143 ± 75 ml/min at the different times of measuring and increasing serum levels of ethanol (mean ± SD, p=0.007). The forearm blood flow of the HPC group rose nonsignificantly from 85 ± 55 to 110 ± 71 and finally 116 ± 56 ml/min (mean ± SD, p=0.2). These values are summarised in *table 2*. Although the increase in forearm flow was significant for both groups there was no significant change between the LPC and HPC group. Baseline diameter of the brachial artery diameter increased progressively but

**Figure 1.** *Change in FMD as function of time. This shows the FMD (±SEM) at baseline (t=0 minutes), after the first three drinks (t=90 minutes) and after six drinks (t=180 minutes). The results are shown for the low polyphenol drink (LPC) and for the high polyphenol containing group (wine, HPC). No statistical difference exists between the two types of beverage at the three different time points (p=0.48 at t=0, p=0.51 at t=90 and p=0.98 at t=180 minutes). The decrease in FMD within each group and for the two groups combined (both) is highly significant (p<0.001).*




not significantly from 4.1 ± 0.7 to 4.5 ± 0.6 and 4.5 ± 0.7 mm (mean ± SD, p=0.4) in the LPC group and from 4.1 ± 0.7 to 4.4 ± 0.8 and 4.4 ± 0.6 mm (mean ± SD, p=0.23) in the HPC group at the three time points.

The net stimulus on the endothelium, expressed as the maximum blood flow evoked by brief forearm occlusion, increased slightly but nonsignificantly (from 288 ± 114 to 350 ± 126 and finally 350 ± 126 ml/min in the HPC group, p=0.26 and from 243 ± 142 to 282 ± 142 and finally 282 ± 54 ml/min in the LPC group, p=0.23). To show the net effect of alcohol on FMD a regression plot was constructed for delta (begin – endpoint) FMD *vs* delta alcohol. A significant correlation was found (r=0.46, p=0.04) for both the HPC and LPC group (*figure 2A*).

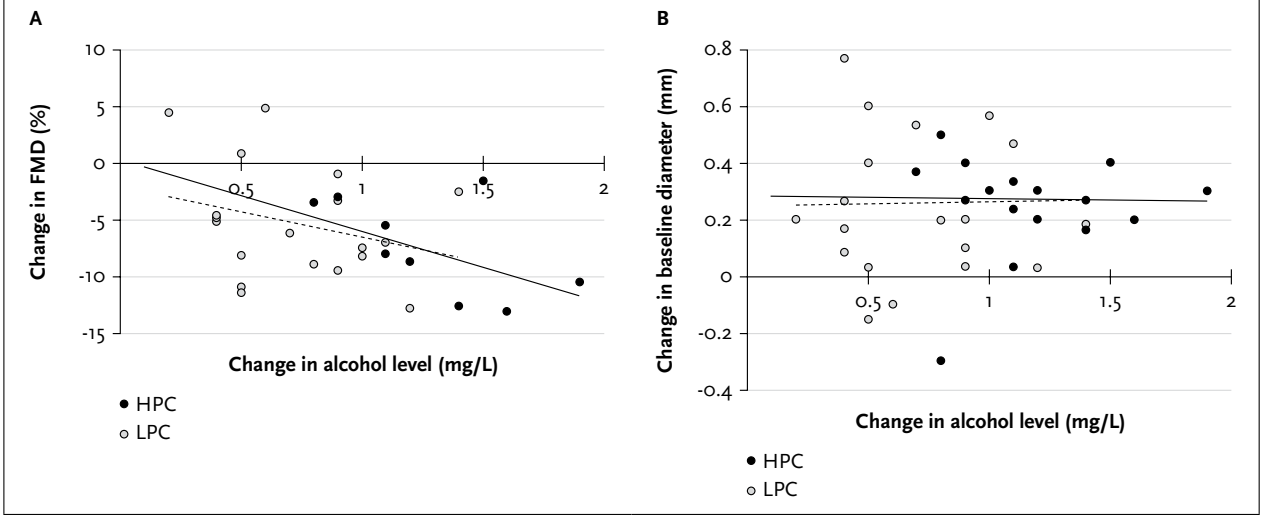
The formula for FMD depends on the baseline diameter, as the artery's capacity to dilate reciprocally diminishes with its diameter. The decrease in the observed FMD could therefore be caused by an increase in baseline diameter. A graph was constructed for delta baseline diameter *vs* the delta alcohol (*figure 2B*). The baseline diameter in both the HPC and LPC group increased somewhat but this did not seem to correlate with the change in alcohol level (r=0.05, p=NS). The observed decrease in FMD appears to be, at least partially, explained by an increase in baseline diameter.

**Table 2.** *Changes in alcohol, routine haematology, chemistry, and markers of inflammation in plasma and FMD.*

| | LPC | | | HPC | | | |
|---|---|---|---|---|---|---|---|
| | t=0 | t=90 | t=180 | t=0 | t=90 | t=180 | P value |
| Alcohol concentration (‰) | 0.0 | 0.5 (0.2) | 0.96 (0.2) | 0.0 | 0.58 (0.2) | 1.25 (0.3) | NS |
| **Haematology** | | | | | | | |
| Haemoglobin (mmol/l) | 8.5 (1.1) | 8.4 (1.0) | 8.4 (1.1) | 8.4 (0.9) | 8.5 (1.0) | 8.4 (1.2) | NS |
| Haematocrit(l/l) | 0.39 (0.04) | 0.39 (0.04) | 0.39 (0.05) | 0.39(0.04) | 0.39 (0.04) | 0.39 (0.06) | NS |
| **Chemistry** | | | | | | | |
| Creatinine (μmol/l) | 79.4 (12.1) | 78.6 (15.1) | 76.0 (13.4) | 75.9 (11.6) | 72.6 (10.3) | 68.2 (12.6) | NS |
| Glucose (mmol/l) | **5.8 (0.9)** | **7.2 (1.7)** | 7.6 (2.0) | 5.5 (0.8) | 4.8 (0.5) | 4.8 (0.3) | p<0.004¶ |
| ALAT (U/l) | 25.5 (8.5) | 24.8 (7.8) | 22.5 (9.2) | 21.5 (9.1) | 22.8 (9.8) | 22.2 (10.1) | NS |
| ASAT (U/l) | 16.0 (4.3) | 15.9 (2.8) | 15.2 (3.4) | 16.8 (4.8) | 17.8 (8.5) | 17.3 (6.3) | N |
| γGT (U/l) | **14.9 (5.3)** | 14.3 (5.0) | 12.7 (4.7) | **20.0 (17.0)** | 19.9 (17.5) | 20.7 (18.4) | p<0.05* |
| **Lipids** | | | | | | | |
| Cholesterol (mmol/l) | 4.82 (0.8) | 4.74 (0.8) | 4.54 (0.8) | 4.68 (1.1) | 4.75 (1.2) | 4.77 (1.0) | NS |
| Apolipoprotein A1 (g/l) | 1.42 (0.29) | 1.44 (0.24) | 1.40 (0.21) | **1.31(0.28)** | **1.06 (0.17)** | 1.09 (0.17) | p<0.05 ** |
| Apolipoprotein B (g/l) | 0.79 (0.14) | 0.76 (0.17) | 0.75 (0.14) | 0.80(0.21) | 0.83 (0.32) | 0.87 (0.32) | NS |
| HDL cholesterol (mmol/l) | 1.42 (0.38) | 1.39 (0.36) | 1.32 (0.33) | 1.21(0.33) | 1.22 (0.36) | 1.25 (0.31) | NS |
| LDL cholesterol (mmol/l) | 2.87 (0.53) | 2.72 (0.54) | 2.64 (0.57) | 2.79(0.74) | 2.80 (0.73) | 2.84 (0.65) | NS |
| Triglycerides (mmol/l) | 1.22 (0.66) | 1.39 (0.66) | 1.30 (0.64) | 1.53(0.84) | 1.61 (0.90) | 1.49 (0.82) | NS |
| **Miscellaneous** | | | | | | | |
| C-reactive protein (mg/l) | 5.9 (1.7) | 6.0 (1.9) | 5.2 (0.7) | 6.4 (2.3) | 7.1 (3.2) | 6.2 (2.0) | NS |
| Mannose binding lectin (mg/l) | 1.49 (1.17) | 1.43 (1.12) | 1.49 (1.31) | 1.31(0.76) | 1.10(0.79) | 1.22 (0.90) | NS |
| **Measurements** | | | | | | | |
| FMD (% change) | 7.3 (4.8) | 2.8 (2.9) | 1.2 (3.3) | 8.6 (1.8) | 1.8 (3.7) | 1.2 (2.6) | NS |
| Baseline diameter (mm) | 4.1 (0.7) | 4.5 (0.6) | 4.5 (0.7) | 4.1 (0.7) | 4.4 (0.8) | 4.4 (0.6) | NS |
| Flow (ml/min) | **54 (40)** | 87 (41) | **143 (75)** | 85 (55) | 110 (71) | 116 (56) | p<0.05 # |
| Heart rate (bpm) | 71 (8) | 73 (8) | 77 (14) | 61 (7) | 59 (8) | 63 (7) | NS |
| Mean arterial pressure (mmHg) | 117 (10) | 111 (9) | 109 (12) | 111 (12) | 112 (17) | 115 (11) | NS |

**Values are means with SD in brackets. NS = not significantly different; ¶ = a significant increase in glucose levels was observed in the LPC groups after three drinks because of the high glucose contents of the drinks. * The γGT levels in the HPC count were significantly higher than in the low polyphenolic group, this was due to one volunteer. ** For unknown reasons apolipoprotein A1 decreased significantly in the HPC group. # Flow increased significantly in the LPC group after 6 drinks (t=180 minutes).**

**Figure 2.** *The change in FMD as function of change in alcohol level during the entire experiment (t=90 and t=180 minutes) is shown in figure 2A. This is a significant decrease as can be observed from the trend lines (r=0.46, p=0.04). The dark line represents the HPC group and the dotted line the LPC group. The difference of the baseline diameter in relation to the increase in alcohol level is shown in figure 2B. Though there is an increase in the average baseline diameter, this relation is not significant. Nor is there a significant correlation between alcohol concentration and increase in baseline diameter (r=0.06, p=NS).*




**Heart rate and conduction times during the experiment**

Heart rate (HR) for the two groups combined (n=20) did not increase significantly from 66.6 ± 9.2 to 66.3 ± 10.6 and 70.7 ± 13 beats/min (mean ± SD, p=0.07) and plotting the changes in HR *vs* the changes in ethanol levels did not show a relation (r=0.05, p=NS). Delta alcohol *vs* delta PQ time showed a trend to significance (r=0.43, p=0.06, results not shown in *table 2*).

**Blood pressure during the experiment**

Blood pressure of both groups combined remained virtually constant during the experiment, showing no significant change after the first three drinks (MAP 114.8 ± 12 *vs* 111.6 ± 13 *vs* 112 ± 12 mmHg (mean ± SD; *table 2*).

**Alcohol-induced changes in serum levels of risk factors for CVD**

For unknown reasons apolipoprotein A1 levels dropped significantly after three glasses of red wine. No other significant changes were seen in any of the monitored lipid fractions (HDL, LDL, and total triglycerides), or in the inflammation parameters evaluated (CRP and mannose binding lectin) that are more associated with cardiovascular disease than normal CRP (*table 2*); we did not measure high sensitive CRP levels.

**Glucose concentrations during the experiment**

Glucose levels rose significantly from 5.8 to 7.6 mmol/l in the LPC group (p<0.001), whereas no significant change was observed in the HPC group (from 5.5 to 4.8 mmol/l). *Table 2* summarises the values obtained.

## DISCUSSION

Our experiment shows that binge drinking, even at socially accepted levels, produces profound changes in haemodynamics irrespective of polyphenolic content of the beverage. Binge drinking increased baseline forearm flow but heart rate and blood pressure remained stable. More importantly, rapid consumption of alcohol decreased flow-mediated vasodilation in our experiment. This contradicts previous reports of beneficial effects of moderate and prolonged alcohol consumption on FMD in patients with coronary artery disease[18-20] and improvement of FMD after consumption of red wine.[6-9]

Some differences in design and selection of subjects might have contributed to these differences. Of note, most trials with alcohol and FMD have been performed in patients with established coronary artery disease.[18-20] It is known that patients with coronary artery disease have endothelial dysfunction, which is related to cardiovascular outcome within five years of follow-up. We, on the other hand, used healthy volunteers, which might explain some differences in FMD measurements.[17] More important is that most trials were performed with a longer follow-up. This allows the metabolic effects of alcohol or polyphenol-induced modulations in gene expression to take place.[1] However, binge drinking presumes cessation of alcohol consumption after the binge. Therefore, long-term beneficial effects of metabolism or gene expression will not take place after a binge. Furthermore, previous studies performed on healthy volunteers corroborate our results and showed that a four-week exposure to alcohol did not change FMD,[21] but increased blood pressure.[22]

Few studies have actually looked at FMD after acute ingestion of alcohol. We found that alcohol actually decreased FMD. This is in agreement with a previous study that observed a small decrease in FMD after consumption of Japanese vodka.[7] In contrast to this previous study we did observe a decrease in FMD after consumption of red wine, while they described improvement. However, our volunteers drank more red wine (on average 3.15 mg alcohol/kg). It might be that the alcohol intake opposes the beneficial effects of the red wine polyphenols, while at a lower alcohol count such effects might still be discernable. This theory is corroborated by the fact that the FMD is improved when de-alcoholised wine is consumed, but is unaltered when red wine containing alcohol is consumed.[6]

We showed that increasing levels of alcohol decreased the FMD. However, this decrease cannot be explained by an increase in basal diameter alone. Firstly, a direct relation was observed between the change in FMD and the change in ethanol concentration, whereas no such relation was found for basal diameter. Secondly, the baseline flow was slightly increased, which should have resulted in a higher FMD. It is difficult to translate our results to other publications. For example, the net FMD values observed in our experiment were less than the average values of our historical controls that received sublingual nitroglycerin as an exogenous NO donor. However, the FMD values were somewhat higher than in a previous reported trial of alcohol consumption and FMD.[21] Again, this might be partially explained by the selection of subjects and study methods.

Plasma concentrations of polyphenols are known to peak at approximately 30 minutes after oral administration.[16] In our experiment we could not show a higher FMD in the group that consumed a high polyphenolic drink, although we measured FMD at the moment when the plasma level of polyphenols should have been high. Despite variable absorption of red wine polyphenols from the gut,[16] previous studies have shown a positive effect of wine consumption on FMD.[6] However, in a cross-over study of 16 healthy volunteers high or low intake of alcohol lasting four weeks did not influence FMD.[21]

Our results question the potential of polyphenols in wine to counteract endothelial dysfunction. It appears that the decrease in FMD caused by this amount of alcohol is not compensated by polyphenols. Knowing that the absorption of polyphenols is poor, it might be that the peak concentrations after a binge are insufficient to compensate the decrease of FMD.[16] However, in some trials acute consumption of red wine or de-alcoholised red wine showed improvement of the FMD.[6-9,18,23]

The strength of this study is that the volunteers in our experiment consumed a large amount of alcohol and wine in a short period: a binge. This closely resembles the drinking patterns of the modern youth[2] and is possibly more related to cardiovascular events than a moderate consumption of alcohol and red wine.[22] Furthermore, the subjects were young, healthy adults and not patients with proven coronary artery disease, who might benefit more from cardioprotection. It appears that especially young males have drinking patterns, like binge drinking, that put them at risk for cardiovascular disease while not having any other cardiovascular risk factors.

Some comments have to be made on the methodology of this study. This study used a healthy, young volunteers in a non-cross-over design. Yet, the number of volunteers is comparable to previous studies on this subject.[6-9] Additionally, we did not include a control group, consuming no alcohol but only water. We therefore have no control for the time element or the possible influence of consuming a drink. However, in our experience, the influence of time, taking an interval between FMD measurements of one hour, is negligible, while in our pilot study no effect of drinking water on FMD could be demonstrated. This is corroborated by another study on FMD that showed no influence of water consumption on FMD up to 120 minutes.[24]

A second consideration is that the volunteers in the low LPC group had increased levels of glucose during the experiment. This is caused by the higher glucose content of the LPC drinks. The effects of a high glucose count on FMD are somewhat conflicting. Acute high glucose levels are known to influence FMD, though high carbohydrate diets have been shown not to influence FMD.[25] If anything, this increased glucose level should actually augment the difference in FMD with the HPC group, an observation we could not confirm in our experiment.

A third consideration is that although we tried to standardise the FMD test as much as possible, we can not exclude influence of some 'external' factors, such as sympathetic activation. Various reports in literature show that activation of the sympathetic nervous system might decrease FMD, although some claim that it has different effects on the baseline brachial artery diameter and that a blunted FMD is not a general response.[26]

Our study shows that alcohol consumption produces vasodilation at both the arteriolar level, indicated by the rise in unstimulated forearm flow, and at the level of a distribution artery. As the mean arterial pressure and heart rate did not change significantly, this change in cardiac afterload is possibly compensated by an increase in stroke volume. The consumption of alcohol at these levels might therefore increase cardiac work, which together with the induction of endothelial dysfunction may play a role in the observed increase in cardiovascular mortality.[14,27] Binge drinking refers to heavy drinking on a single drinking occasion or drinking heavily and continuously over a number of days or weeks, abstaining and then repeating the cycle. These modern drinking patterns in young healthy adults might just expose them to all the cardiovascular risks without any of its benefits.

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CASE REPORT

# Cisplatin-induced hyperglycaemic hyperosmolar coma

**R. Komdeur*, J. Derksen, M-C. Legdeur, B.S. Hylkema**

Department of Internal Medicine, Medical Spectrum Twente Hospital, Enschede, the Netherlands,
*corresponding author: tel.: +31 (0)53-487 20 00, fax: +31 (0)487 30 71,
e-mail: R.Komdeur@ziekenhuis-mst.nl

## ABSTRACT

**We present a case of severe hyperglycaemic hyperosmolar derangement after treatment with cisplatin in a patient without previous diabetes mellitus. Limited data are available on this adverse reaction, explaining why impaired glucose handling due to cisplatin is not generally recognised.**

## KEYWORDS

Cisplatin, diabetes mellitus, hyperosmolar coma

## CASE REPORT

A 43-year-old man with a T2bN1M0 squamous cell carcinoma of the oropharynx was treated with cisplatin (*cis*-diamminedichloroplatinum (II), CDDP) 100 mg/m$^2$ intravenously once every four weeks with concurrent radiotherapy (35 fractions of 2 Gy). The patient was prehydrated to reduce cisplatin nephrotoxicity. Dexamethasone 10 mg was administered intravenously on the cisplatin infusion days and 8 mg orally on the three subsequent days as antiemetic therapy.

Six days after the third cycle of cisplatin the patient was admitted in a lethargic state. His temperature was 38.0 °C; blood pressure was 110/60 mmHg with a pulse rate of 110 beats/min. The skin and mucosal layers were desiccated. Laboratory analysis of the serum revealed hyperglycaemia, hypernatraemia, increased osmolality and impaired renal function (*table 1*). Arterial blood gas analysis showed no abnormalities (*table 1*). Ketonuria was absent. All in all, the patient had developed a severe hyperglycaemic hyperosmolar state, even though he had no history of glucose intolerance, had a body mass index of 21 and his prior renal function tests had been normal. Furthermore, family history revealed no diabetes mellitus. Autoantibodies to pancreatic islands, insulin and glutamic acid decarboxylase, which is linked to (preclinical) type I diabetes mellitus, were not detectable. Treatment was initiated with intravenous insulin and fluid administration. However, shortly after arrival, the patient became comatose, resulting in respiratory failure and a subsequent need for intubation and mechanical ventilation. After normalisation of the internal homeostasis and weaning from the ventilator, the patient persistently required insulin treatment during the next months of follow-up.

## DISCUSSION

In this patient without a pre-existing glucose intolerance and no risk factors for diabetes type 1 or 2, we searched for treatment-related causes of the hyperglycaemic derangement. Because cisplatin is highly emetogenic, glucocorticoids are often prescribed as adjuncts; these drugs are well known for their diabetogenic action. However, glucocorticoid-induced diabetes generally occurs in persons with an impaired glucose metabolism, which is hallmarked by reversibility after discontinuing the drug. Moreover, the low levels of insulin and C-peptide relative to the glucose concentration as in the described case (*table 1*) point toward an insulin deficit rather than the insulin resistance observed with glucocorticoid use.[1,2] Taken together, these findings preclude a glucocorticoid-induced event.

Cisplatin is an inorganic platinum compound that is widely used for the treatment of a variety of tumours, including head and neck carcinoma. Cisplatin is believed to exert its anticancer activity by forming cross-links with DNA, thereby impairing DNA replication, transcription and repair, ultimately leading to cell death.[3] Nephrotoxicity and neurotoxicity are the most common adverse reactions.

**Table 1.** *Laboratory analysis of serum obtained at presentation*

| | Measured value | Reference value |
|---|---|---|
| Glucose | 67.9 mmol/l | 4.0 - 7.8 mmol/l |
| Sodium | 162 mmol/l | 135 - 145 mmol/l |
| Potassium | 3.9 mmol/l | 3.5 - 5.0 mmol/l |
| Urea nitrogen | 27.4 mmol/l | 2.5 - 6.7 mmol/l |
| Creatinine | 151 mmol/l | 70 - 110 mmol/l |
| Osmolality | 423 mosmol/kg | 275 - 300 mosmol/kg |
| pH | 7.39 | 7.36 - 7.44 |
| $pCO_2$ | 5.6 kPa | 4.5 - 6.0 kPa |
| $pO_2$ | 11.0 kPa | 10.0 - 13.3 kPa |
| Bicarbonate | 25 mmol/l | 21 - 27 mmol/l |
| Oxygen saturation | 0.95 mol/mol | 0.95 - 0.98 mol/mol |
| Insulin | < 20.0 mU/l | |
| C-peptide | 0.81 mmol/l | 0.2 - 1.2 mmol |

Hyperglycaemia due to cisplatin in humans remains under-recognised; however, in a retrospective study, 11 of 202 (5%) cancer patients developed diabetes after receiving cisplatin.[4] These patients had received 100 mg/m² cisplatin and hyperglycaemia was documented after a median period of 19 days after treatment, ranging from 7 to 30 days. In this study, two patients presented with hyperosmolar coma; both required insulin treatment from then on.

The mechanism of diabetes mellitus due to cisplatin in humans is obscure. Animal studies demonstrate that cisplatin impairs insulin secretion, possibly by induction of somatostatin and nitric oxide.[5,6] As insulin requirement persists in cases of hyperglycaemic hyperosmolar coma, permanent alterations in glucose metabolism due to cisplatin appear to have occurred. Of interest, pancreatic β-cell function is protected against toxic insults by thioredoxin, an ubiquitous protein involved in balancing the cellular reductive-oxidative state. Thioredoxin prevents rats from developing diabetes after exposure to streptozotocin, a cytotoxic drug used in a classical animal model to elicit diabetes mellitus, but also attenuates cisplatin toxicity.[7] When this protective mechanism fails, it appears conceivable that permanent damage can arise, leading to lasting β-cell dysfunction.

## CONCLUSION

When assessing the probability scale as proposed by Naranjo *et al.*, we designate the presented case of a severe hyperglycaemic hyperosmolar coma as a 'probable' adverse reaction of cisplatin.[8] The low levels of insulin and C-peptide, and the ongoing insulin requirement are indicative of a contributory role for cisplatin. Still, limited data exist on the development of diabetes mellitus in humans after cisplatin treatment and hyperglycaemic hyperosmolar derangement currently remains an unlisted adverse reaction. Given the frequent concomitant use of glucocorticoids, cases of cisplatin-related diabetes mellitus may have been wrongly attributed to these drugs. Therefore, the presented case has been reported to the Netherlands Pharmacovigilance Centre (Lareb). We advise regular (self-) monitoring of serum glucose levels to prevent patients receiving cisplatin to develop such a detrimental condition.

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CASE REPORT

# Therapeutic hypothermia after prolonged cardiopulmonary resuscitation for pulseless electrical activity

**M. Bartels, D.H.T. Tjan, E.M. Reusen, A.R.H. van Zanten***

Department of Intensive Care, Gelderse Vallei Hospital, Ede, the Netherlands, *corresponding author, tel.: +31 (0)318-43 41 15, fax: +31 (0)318-43 41 16, e-mail: zantena@zgv.nl

## ABSTRACT

**We report an 18-year-old female patient with cardiac arrest due to pulseless electrical activity caused by a massive pulmonary embolism. Cardiopulmonary resuscitation was continued for more than one hour. Although the initial clinical signs and symptoms suggested poor outcome, immediate intravenous thrombolysis was instituted. After return of spontaneous circulation (75 minutes) the patient was still comatose and mild therapeutic hypothermia (32.5 °C) was instituted for brain protection during the first 24 hours. She recovered uneventfully without neurological deficit. Therapeutic hypothermia may be effective for neuroprotection in non-VF cardiac arrest.**

## KEYWORDS

Therapeutic hypothermia, induced hypothermia, cardiopulmonary resuscitation, pulseless electrical activity, pulmonary embolism

## INTRODUCTION

Cardiac arrest with global cerebral ischaemia may lead to severe postanoxic encephalopathy and neurological impairment. Several studies have shown that moderate therapeutic hypothermia to a temperature of 32 to 33 °C can reduce brain damage after prehospital cardiac arrest due to ventricular arrhythmia without significant side effects.[1,2] The benefits of therapeutic hypothermia after cardiac arrest due to other causes has not been demonstrated convincingly.[3,4]

We present a young female who underwent cardiopulmonary resuscitation (CPR) for pulseless electrical activity for more than one hour. She presented with extremely unfavourable clinical signs and symptoms for survival and high risk of poor neurological outcome. She was treated with therapeutic hypothermia after return of spontaneous circulation.

## CASE REPORT

An 18-year-old female underwent knee surgery three weeks before emergency admission. She had been complaining of dyspnoea and cough for one day before she collapsed at home. Although witnessed by her family, no adequate basic life support was commenced until the ambulance arrived seven minutes later. Extreme bradycardia with no output was noted as a sign of pulseless electrical activity. Immediate basic life support was started by paramedics on arrival. A total of 5 mg of adrenaline (epinephrine) IV was administered during CPR. The patient was endotracheally intubated and transported to the hospital. On arrival to the emergency room, the patient was still in pulseless electrical activity. Initial end-tidal $CO_2$ was 0.2 kPa. Arterial blood gas analysis showed severe respiratory and metabolic acidosis with severe hypoxaemia: pH 6.60 (7.35-7.45), $pCO_2$ 14.5 kPa (4.5-6.0 kPa), $HCO_3$- 10.2 mmol/l (22-26 mmol/l), $pO_2$ 4.1 kPa (9.5-13.0 kPa), and $SaO_2$ 16% (92-99%). Arterial lactate was 21.0 mmol/l (0.5-1.7 mmol/l). Prompt thrombolysis with rTPA and subsequent intravenous heparin were instituted for suspected massive pulmonary embolism. On transthoracic echocardiography significant right ventricular distension with collapse of the left ventricle was noted. An electrocardiogram showed supraventricular tachycardia, right-axis deviation, and right bundle branch block. D-dimers were 18.70 μg/ml (0.1-0.5 μg/ml). After thrombolysis, spontaneous circulation returned 75 minutes after arrest and capnographic $CO_2$ elimination increased to normal. The blood pressure improved with vasopressors (dopamine and noradrenaline). Blood gases and lactate levels normalised within six hours.

On ICU admission, the patient was still comatose (Glasgow coma scale 3). Hypothermia was induced according to our

institutional cooling protocol (*figure 1*), using rapid infusion of two litres of ice-cold saline (4 °C) and two cooling mattresses (Blanketroll II, CSZ, Cincinatti, USA). Temperatures were continuously measured using an oesophageal temperature probe. A target temperature of 32.5 °C was reached within 120 minutes and continued for 24 hours (*figure 2*). Cefotaxime was started for suspected aspiration.

Significant electrolyte disorders (phosphate 0.58 mmol/l (0.8-1.4 mmol/l), $Ca^{++}$ 1.04 mmol/l (1.15-1.29 mmol/l), $K^{+}$ 3.4 mmol/l (3.5-4.7 mmol/l), $Mg^{++}$ 0.69 mmol/l (0.7-1.1 mmol/l) and metabolic derangement (glucose 12.2 mmol/l (4.0-10.0 mmol/l)) as side effects of therapeutic hypothermin were observed. Minor bleeding occurred from mucosal areas and puncture sites due to the combination

**Figure 1.** *Therapeutic hypothermia protocol*

**Selection criteria**
Patients with cardiac arrest of any cause and location (IHCA/OHCA)
Return of spontaneous circulation
Comatose (Glasgow Coma Scale < 8)

↓

**Induction phase**
Sedation with propofol or midazolam and morphine, in case of severe chills add bolus rocuronium
Rapid infusion of 2 litres of cold (4 °C) NaCl 0.9%
Two cooling mattresses (Blanketroll II, CSZ) underneath and on top of the patient, temperature set at 4 °C until temperature 34 °C is reached, then set at 32.5 °C
Supplementation of 2 g magnesium sulphate iv

↓

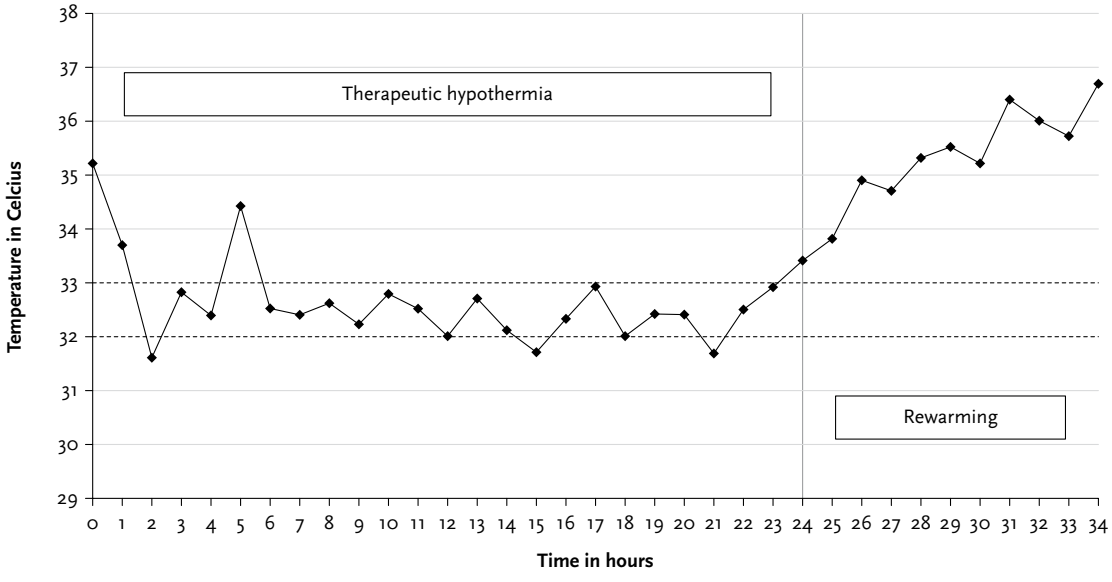
**Hypothermia maintenance phase**
Maintenance of therapeutic hypothermia with cooling mattresses set at temperature 32.5 °C for 24 hours
Continuation of sedation

↓

**Rewarming phase**
Rewarming rate of 0.3 °C per hour to target temperature of 36 °C
Discontinuation of sedation after reaching normal temperature
Preservation of normal temperature during 24 hours, using cooling mattress and/or antipyretics

**Laboratory investigation during therapeutic hypothermia**
During first 6 hours every 2 hours, thereafter every 4 hours: potassium, calcium, magnesium, phosphate, glucose, arterial blood gas
Once daily: complete blood count, renal functions, amylase, liver enzymes, prothrombin time, activated partial thromboplastin time

**Figure 2.** *Oesophageal temperatures during induction, maintenance and rewarming phase*




Bartels, et al. Therapeutic hypothermia for pulseless electrical activity.

of thrombolysis, heparinisation and probably additional coagulation disturbances due to therapeutic hypothermia.
After 24 hours of hypothermia, the patient was rewarmed at a rate of 0.3 °C per hour to a temperature of 36 °C. Subsequently, sedation was discontinued to assess the neurological status. She fully recovered without neurological impairments one day after cessation of sedation and could be extubated successfully. She was speaking coherently. Only slight disturbances in short-term memory were noted, although an electroencephalogram showed diffuse excessive slow theta activity as a possible sign of postanoxic disturbances. A computed tomography of the chest was performed to detect possible residues of the pulmonary embolism. Only small peripheral perfusion defects were visible, consistent with the clinical picture of successful thrombolysis.
The patient was transferred to the general ward. Further recovery was uneventful. Fourteen days after admission she was discharged. Her cerebral performance category (CPC) score was 1.[5]

## DISCUSSION

Our patient survived pulseless electrical activity due to massive pulmonary embolism after successful thrombolysis. The (neurological) recovery is remarkable since the delay in basic life support, the duration before return of spontaneous circulation, the severity of lactic acidosis and initial coma score suggested a high risk of severe postanoxic encephalopathy. In contrast to this, neurological outcome was beneficial (CPC 1).
Furthermore, prognosis of circulatory arrest due to other causes than ventricular fibrillation is very poor. Reports thus far have not proven convincingly that benefits in outcome of therapeutic hypothermia for arrests other than ventricular arrhythmia are relevant, although animal data suggest similar effects on cerebral protection in both VF and non-VF arrest.[6,7]

Postanoxic encephalopathy is a common complication after cardiac arrest. Only 5% of all out-of-hospital arrests with cardiac aetiology are discharged with a favourable neurological outcome.[8] Several factors in the reperfusion phase contribute to cerebral damage that adds to the ischaemic injury during circulatory arrest.
First, although circulation is restored, there may be a continued and inhomogeneous hypoperfusion of the brain. Second, release of certain amino acids (most notably glutamate) leads to excitotoxicity. Oxygen free radicals trigger chemical cascades causing further damage. This may lead to apoptosis and/or necrosis. Finally, extracerebral causes such as metabolic derangements and organ failure due to circulatory arrest can add to the development of postanoxic encephalopathy.[9]

The exact mechanisms by which hypothermia protects the brain during reperfusion are as yet unknown. The beneficial effects may be mediated through a decrease in metabolism and oxygen demand. Animal studies show that hypothermia attenuates the release of excitatory amino acids and improves cerebral perfusion.[7,10,11]
Several cooling techniques are available.[12] Early induction of hypothermia is important to enhance optimal cerebral protection.[6] In our experience target temperatures can be rapidly reached with cold infusions (time to target temperature 60-120 min) and acceptably maintained using surface cooling devices. Furthermore, rewarming can be controlled using such a cooling device, as passive rewarming may be too rapid and induce reperfusion damage to the vulnerable areas of the brain.
There are no absolute contraindications for therapeutic hypothermia, although several complications have been documented. Most frequently immunodepression, thrombocytopenia and coagulation disorders, arrhythmia, electrolyte abnormalities, lactic acidosis, hyperglycaemia, pancreatitis, and polyuria are reported.[7] In the critical care environment most of these complications may be circumvented by frequent observations and laboratory measurements, and after institution of adequate therapeutic interventions.

## CONCLUSION

Therapeutic hypothermia may be beneficial for neuroprotection in cardiac arrest patients due to other causes than ventricular fibrillation. Our observations warrant further research in this area.

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Netherlands
The Journal of Medicine

PHOTO QUIZ

# An unusual cause of hypertrichosis

**M.T.C. Pruijm[1*], W.H. van Houtum[2]**

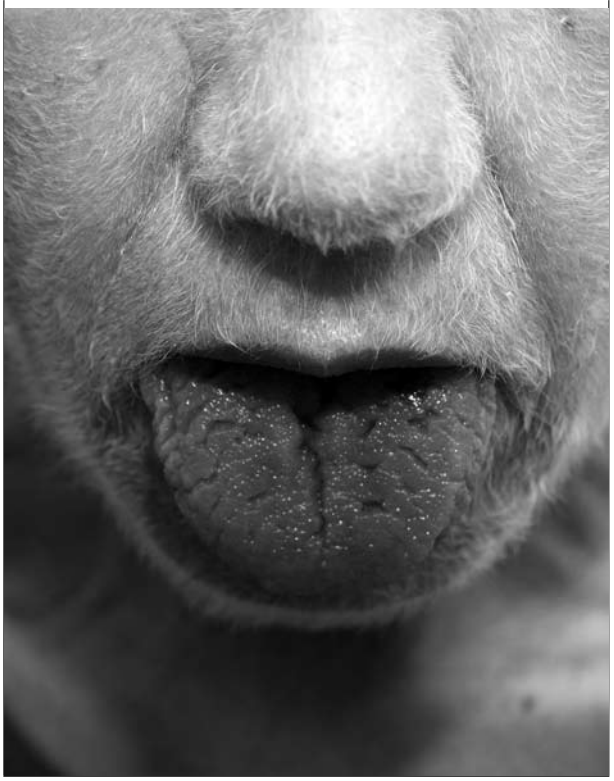
[1]Centre Hospitalier Universitaire Vaudois (CHUV), Department of Nephrology, Lausanne, Switzerland, [2]Department of Internal Medicine, Spaarne Hospital Hoofddorp, [*]corresponding author: tel. and fax: 0041-22-300 60 14, e-mail: mennopruijm@hotmail.com

A 58-year-old woman presented with a three-month history of an increase in body hair. Her tongue had been reddish with a burning sensation for one year. In the previous months she had lost ten kilos, accompanied by diarrhoea. The patient had had endometrial carcinoma stage III two years before presentation, for which a hysterectomy and local radiotherapy had been performed. Physical examination revealed multiple fine, long, non-pigmented hairs located on the face, behind her ears, on her shoulders and arms. Besides a glossitis no other anomalies were noted.

## WHAT IS YOUR DIAGNOSIS?

See page 45 for the answer to this photo quiz.

**Figure 1.**



LETTER TO THE EDITOR

# Mesothelioma: a case report

*We would like to take issue to two points raised by Vestjens et al.[1]*

*1. Based on a 16-year-old article on seven cases, the condition may indeed be rare. However, using the Internet we noticed that peritoneal mesothelioma is the second most frequent primary malignancy associated with asbestos, with 100 to 500 new cases in the USA each year (approximately 10 to 20% of all asbestos-associated malignancies).[2] Studies including hundreds of patients have been published.[3-5] It may be true that diagnosing an abdominal mesothelioma is difficult due to the nonspecific presentation and mild symptoms of the disease. But lack of familiarity with the condition may further delay the diagnosis as demonstrated in the following case from our own practice.*
*A 69-year-old male patient was followed for over three years in a multi-specialist practice of internal medicine because of intermittent ascites. The results of endoscopies and computerised tomographies were negative while peritoneal paracenthesis gave nonspecific results. A provisional diagnosis of familial Mediterranean fever was made, because a far ancestor was from the Mediterranean. A few weeks ago, he developed symptoms of intermittent subileus of the ileum. At laparoscopy it was very hard to get access to the peritoneal cavity caused by the extremely hard white fibrotic rectus fascia. The ileum was attached to the peritoneum with a lot of scar tissue. A fibrotic white liver was observed. Biopsies were taken from it and from the rectus fascia. Pathological specimens were compatible with a diagnosis of malignant mesothelioma.*

*2. The authors report no history of exposure to asbestos in their patient, a fork-lift truck driver. Some 30 years ago, the latency time given by the authors, asbestos was commonly used in the floors and walls of storehouses for insulation and fire protection. Lorry drivers were particularly at risk due to the continuous dust their work caused. We should add that both our case and that of the authors underline the importance of a thorough history taking. Particularly workers at shipyards, mines, and factories were at risk. Our patient was from the first group, although he had only worked there for two years some 30 years ago. As the latency time has been completed by now for many future patients, we need to be alert. This is relevant since the prognosis is dependent on the stage, with over 90% five-year survival in non-metastasised cases.[2-4] In order to enhance diagnosis making, we recommend the algorithm provided by the Mesothelioma Speciality Group, which is laparoscopy with multiple biopsies guided by CT chest, abdomen, and pelvis,[6] rather than scintigraphic methods, such as those used by the authors.*

**J. van Brakel[1], B. van Ouwerkerk[2], T.J. Cleophas[3]**
[1]co-assistent, Department of Internal Medicine, [2]Department of Endocrinology, [3]Department of Internal Medicine, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands

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6. http://www.surgicaloncology.com/meso.htm

# Response from the authors

*We would like t o thank Van Brakel et al. for their comments on our case report.[1]*
*Although it is the second ranked malignancy associated with asbestos exposure, abdominal mesothelioma still has a really low incidence of 1/1,000,000, as we mentioned. Thus, it will be impossible for us to become familiar with such a disorder. The case report by Van Brakel et al. merely illustrates this point.*
*Thorough history taking will indeed often reveal (a hint of) asbestos exposure. Our patient was 40 years of age at diagnosis, which almost excludes an occupational exposure to asbestos within the latency time of 30 years. Furthermore, it should be emphasised that his first CT was negative, so the question remains whether a vague hint of asbestos exposure could have changed the diagnostic process: does this justify laparoscopy?*
*We feel that our case report demonstrates that in such a patient with fever of unknown origin, Indium-111 scintigraphy is a very elegant, noninvasive method of directing further invasive procedures.*

**J.H.M.J. Vestjens[1*], M.S. Rahnama[1], B.T. Brans[2], J. Buijs[1]**
Departments of [1]Internal Medicine and [2]Nuclear Medicine, Atrium Medical Centre, Henri Dunantstraat 5, 6419 PC Heerlen, the Netherlands, [*]corresponding author: tel.: +31 (0)45-576 66 66, fax: +31 (0)45-571 33 60, e-mail: hannekevestjens@yahoo.com

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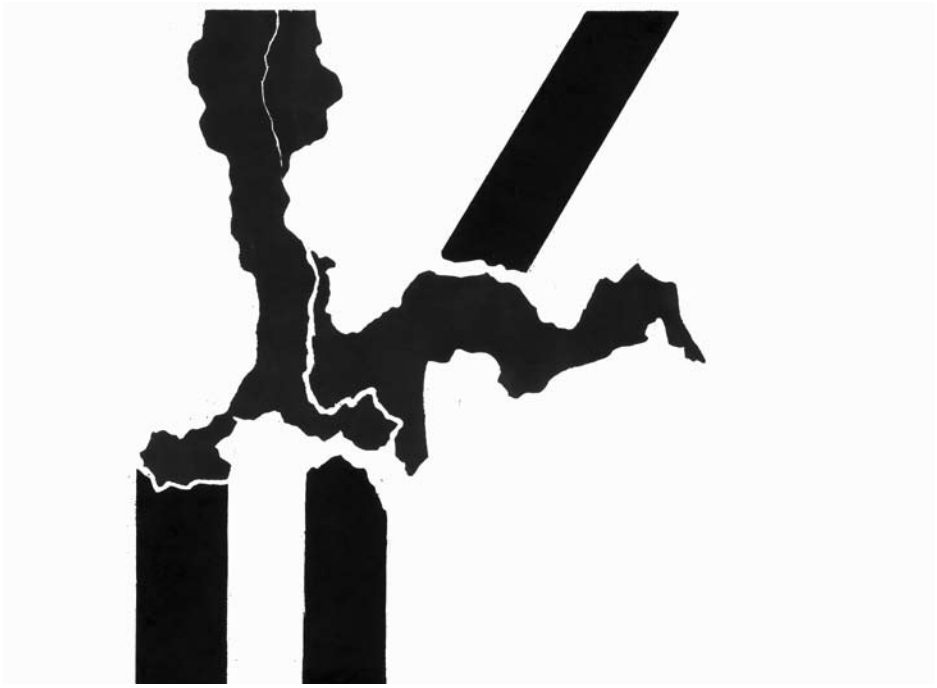
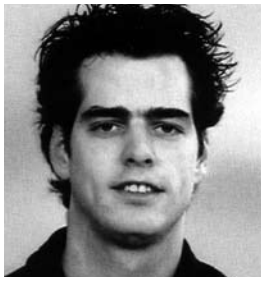
1. Vestjens JH, Rahnama MS, Brans BT, Buijs J. A case of abdominal mesothelioma diagnosed by indium-III leucocyte scintigraphy. Neth J Med 2006;64:157-9.

ABOUT THE COVER

# Untitled

**Camiel Andriessen**





Camiel Andriessen (1974) studied at the Academy of Art in Enschede.
Since 1995, his work can be seen in many exhibitions in the Netherlands and abroad. Successively his art has been exposed at the Grosse Kunstausstellung NRW Düsseldorf, Germany from 1995 till 2000, but also the Xylon exposition in Canada, Brazil, Poland and France and Italy are favourite exhibitions.
His motivation for being a creative artist is the interference between culture and nature in our landscape. Paradoxal beauties scream in silence about their annoyances and provide the basics for his work. His work is a report of this incomprehensible but understandable struggle without a winner. Woodcut is an ideal technique to use to work as directly and expressively as possible. In the wooden plate the basics can be recognised, the interference between nature and culture. With this fact he uses small elements to rearrange them in another chosen setting.

You can order an original print at a price of € 200 from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands, e-mail: galerie-unita@planet.nl, www.galerie-unita.com.

## ANSWER TO PHOTO QUIZ (ON PAGE 42)

## AN UNUSUAL CAUSE OF HYPERTRICHOSIS

The clinical features were consistent with a diagnosis of hypertrichosis lanuginosa acquisita (HLA). Extensive endocrine analysis did not reveal any underlying hormonal overproduction causing the increased hair growth. In search of an underlying malignancy, a CT scan of the abdomen yielded periaortic adenopathies. Transgastric endoscopy-guided puncture confirmed the suspicion of metastatic adenocarcinoma, for which patient was treated with local radiotherapy.

HLA is defined by the presence of lanugo hair in adults. It is an extremely rare, usually paraneoplastic manifestation, most often seen in lung, colon, uterus or breast carcinoma.[1-3] It can precede or follow the malignancy and is often accompanied by glossitis and steatorrhoea, as in our patient.[2] Nonmalignant causes such as anorexia nervosa, AIDS and systemic drugs (cyclosporin, minoxidil) should be excluded.[3]

The underlying mechanism remains unknown, despite many biochemical and hormonal studies in affected patients.

Our patient was treated with locoregional radiotherapy (39 Gy) to the periaortic adenopathies. In the following months, interestingly, the hypertrichosis diminished considerably.

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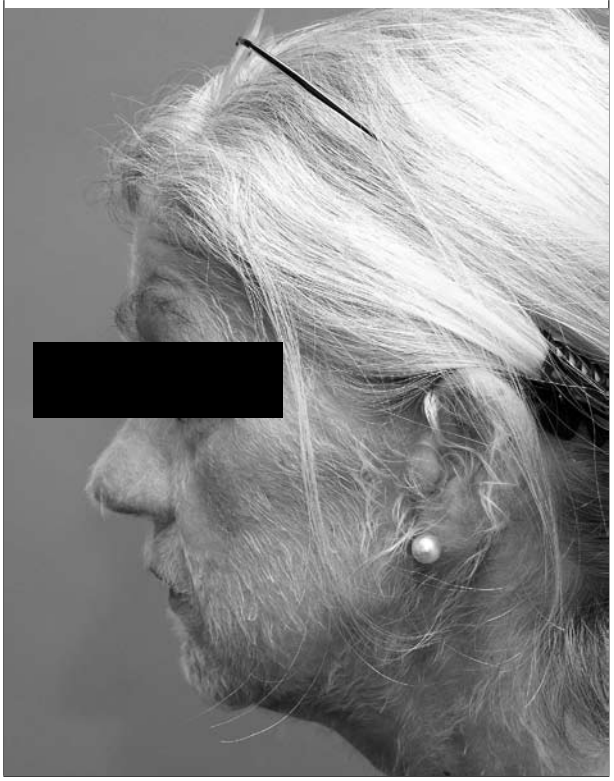
3. Pérez-Losada E, Pujol M, Domingo P, et al. Hypertrichosis. Clin Exp Dermatol 2001;26:182-3.

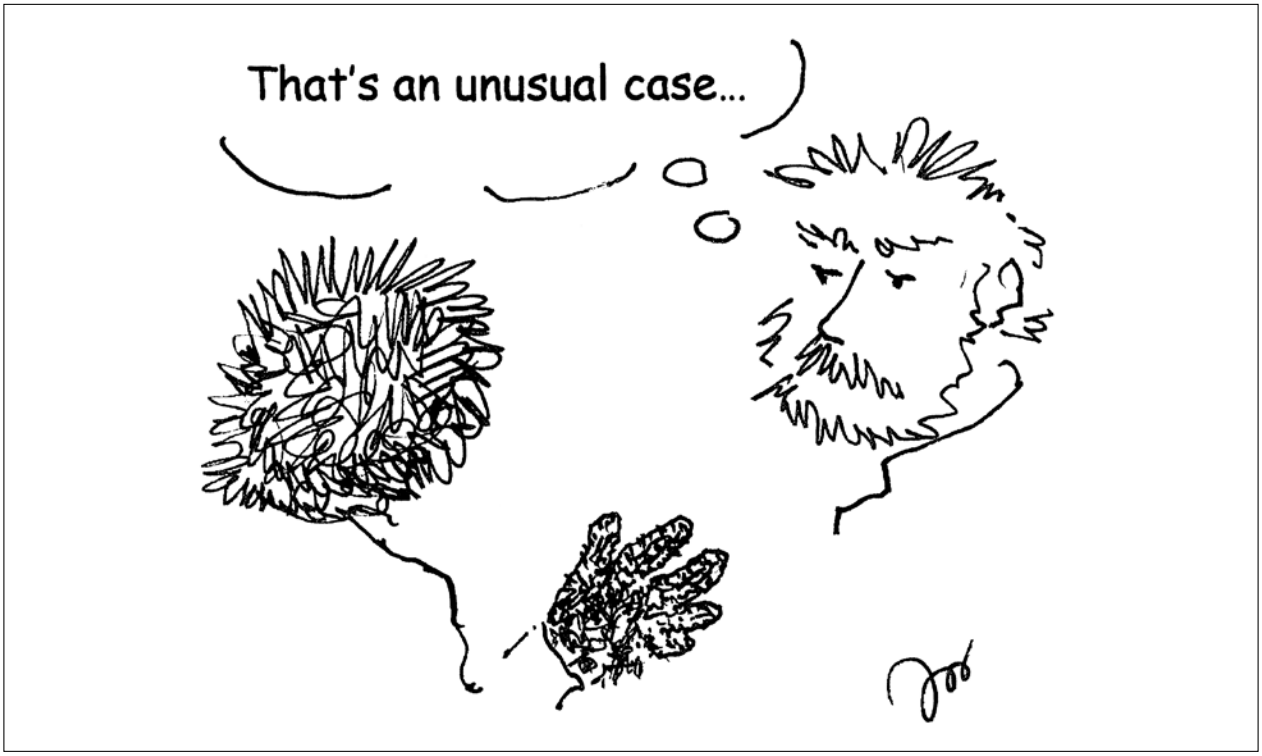
**Figure 2.**



## MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the October 2006 issue of the Netherlands Journal of Medicine. This is based on analysis of our user log file on 13 December, 2006 (www.njmonline.nl)

| Article | Online hits |
|---|---|
| EDITORIAL | |
| Assessment of a new rapid urease test (GUT test) to diagnose *Helicobacter pylori* infection | 89 |
| REVIEWS | |
| Efficacy and safety of inhaled insulin in the treatment of diabetes mellitus | 159 |
| Oxybutynin: dry days for patients with hyperhidrosis | 137 |
| ORIGINAL ARTICLES | |
| Validation of a new, commercially available dry rapid urease test for the diagnosis of *Helicobacter pylori* infection in gastric biopsies | 90 |
| HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre | 109 |
| CASE REPORTS | |
| A therapy resistant vasculitis? | 99 |
| Sarcoidosis mimicking metastatic disease: a case report and review of the literature | 119 |
| Sclerosing peritonitis: an unusual cause of ascites in a patient with systemic lupus erythematosus | 132 |
| PHOTO QUIZ | |
| The ECG in hypothermia: Osborn waves | 123 |
| LETTER TO THE EDITOR | |
| Tension pneumothorax with a patent thoracostomy tube | 86 |
| **Total** | **1143** |



## INFORMATION FOR AUTHORS

**Aims and scope**
The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

**Manuscripts**
Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

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

**Submission**
All submissions to the *Netherlands Journal of Medicine* should be submitted online through Manuscript Central at http://mc.manuscriptcentral.com/nethjmed. Authors should create an account and follow the instructions. If you are unable to submit through Manuscript Central contact the editorial office at g.derksen@aig.umcn.nl, tel.: +31 (0)24-361 04 59 or fax: +31 (0) 24-354 17 34.

**Preparation of manuscripts**
Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process, number the lines in the margin and the pages.
*Subheadings* should not exceed 55 characters, including spaces.
*Abbreviations*: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for generic names of substances and materials.
A *Covering letter* should accompany the manuscript, identifying the corresponding person (with the address, telephone number, fax number and e-mail address). Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. The letter should make it clear that the final manuscript has been seen and approved by all authors. All authors should sign the letter. The letter should either be submitted through http://mc.manuscriptcentral.com/nethjmed or faxed to the editorial office (+31 (0)24-354 17 34).

Divide the manuscript into the following sections: Title page, Abstract, Keywords, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

The *Title page* should include authors' names, degrees, academic addresses, correspondence address, including telephone number, fax number, e-mail address and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

*Keywords*: Include three to five keywords.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely, without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

*Acknowledgement*: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.

*References* should be numbered consecutively as they appear in the text (after the punctuation and in square brackets). Type the reference list with double spacing on a separate page. References should be in the language they are published in, conform the 'Vancouver' style for biomedical journals (N Engl J Med 1991;324:424-8).

Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Examples:

1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against the reference list after your manuscript has been revised.
The use of bibliographic software programmes that are designed to generate reference lists such as Reference Manager© or Endnote© is highly encouraged. Authors can use the predefined output 'Vancouver' style from these programmes.

*Tables* should be typed with double spacing each on a separate page, numbered consecutively with Arabic numerals, and should contain only horizontal lines. Provide a short descriptive heading above each table with footnotes and/or explanation underneath.

*Figures* must be suitable for high-quality reproduction (>300 DPI). Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. Colour figures are occasionally possible and will be charged to the authors.
*Legends for figures* should be typed, with double spacing, on a separate page.

**Case reports**
Case reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Selection of case reports will be based on criteria as outlined in a special report by the editors (Drenth et al. The case for case reports in the Netherlands Journal of Medicine. Neth J Med 2006;64(7):262-4). We advise potential authors to take notice of the instructions in this report. Articles published in this section should be no longer than 1000 words, and supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

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Mini reviews are concise notes that bring the reader up to date with the recent developments in the field under discussion. The review article should mention any previous important reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The manuscript should be divided as follows: title page, abstract and main text. The text may be subdivided further according to the areas to be discussed. The text should not exceed 2500 words.

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