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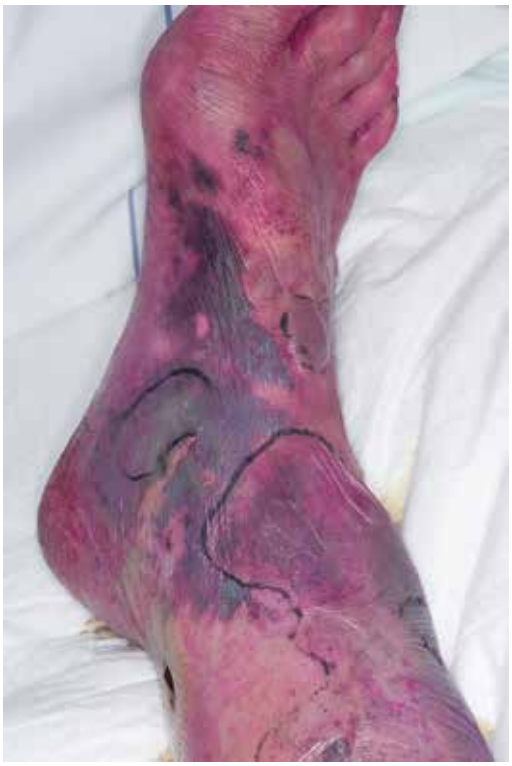

*Barefoot along the shoreline; what is your diagnosis?*



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VAN ZUIDEN COMMUNICATIONS

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EDITORIAL

# Incidental findings; prevention is better than cure

**P.L.A. van Daele[1,2]*, J.L.C.M. van Saase[1]**

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In this issue of the journal Spierings *et al*. describe the results of bone marrow biopsy after detecting incidental signal alterations of bone marrow on MRI performed for musculoskeletal symptoms without clinical suspicion of a haematological disorder. In 7 out of 15 patients a clinically significant haematological disorder was detected.[1]

It is a small study, including only 15 patients, and unfortunately we do not know how many patients in total underwent MRI scanning for musculoskeletal symptoms. But if we assume that incidentally found abnormalities were reported in all patients undergoing an MRI scan, this suggests that once they are detected, bone marrow biopsy is warranted.

Nowadays, incidental findings are becoming more and common with the emergence of sophisticated imaging techniques. Whereas bone marrow alterations might indicate the need for further examination, this may not hold true for other incidentally found abnormalities. As Dr Bluemke in Circulation puts it: 'Because of the comprehensive nature of computed tomography (CT) scanning, incidental findings are found seemingly on almost every CT scan performed for a wide variety of reasons in a radiology department.'[2] For instance, depending on age approximately 5% of people show adrenal nodules on CT scanning.[3] On ultrasound, the imaging modality with the highest sensitivity, the prevalence of thyroid nodules is around 30%.[4] On coronary CT angiography, used to evaluate patients with chest pain, 16% of patients showed pulmonary nodules.[5]

Whether incidental findings need follow-up depends on the presence of underlying risk factors that might increase the a-priori chance of finding significant disease. Surveillance in pulmonary nodules is different in smokers as compared with non-smokers. Nevertheless, the risk of malignancy, or even significant non-malignant disease, in these incidental findings is low, and therefore the benefit of follow-up might not outweigh the costs or the complications associated with the procedures performed.

In the study by Goehler *et al*., they calculated that the follow-up of incidentally found pulmonary nodules in coronary CT angiography resulted in a relative reduction of lung cancer mortality of 4.6% and an improvement of quality-adjusted life expectancy of no more than seven quality-adjusted life-days:[5] statistically significant but far from relevant.

In a recent issue in JAMA Internal Medicine, Dr Barry eloquently illustrates the downside of sophisticated and extensive imaging, demonstrating the effect of follow-up of incidental findings in one of his patients.[6] Ignoring incidental findings might lead to legal and ethical implications. But following up all incidental findings will lead to an increase in medical costs and the risk of unnecessary complications. He proposes to mitigate the problem of incidental findings by limiting scans to the body area of interest.

Unfortunately, posh private clinics offer unnecessary check-ups with MRI and CT scans, allegedly intended to give you peace of mind. But whereas some tests may be beneficial, most are not and some can even do harm.

Incidental findings are not restricted to imaging techniques. There is, for instance, much debate on whether and how incidental findings from next generation sequencing in research studies and patient care should be returned to research participants and patients.[7,8] The American College of Medical Genetics and Genomics (ACMG) recommends that laboratories performing clinical sequencing seek and report mutations present in a list of specific genes (containing for instance mutations in BRCA1 and BRCA2) and the ordering clinician should discuss with the patient the possibility of incidental findings.[9]

And then there is the issue of incidental findings in routine laboratory analysis performed for no obvious reason. Often, when trainees are asked why they perform certain laboratory analyses, the answer is; ' just to be certain'. But inadequate laboratory testing is not a problem restricted to trainees. A study in the United States showed that on average 30% of all laboratory tests are probably unnecessary.[10] And although most laboratory analyses are relatively inexpensive, the resulting sequence of additional studies, when finding results falling out of the normal range, might generate substantial costs and in fact leads to uncertainty for both the doctor and patient. As Dr Arnaout states it: 'In ordering blood tests, we too often tend to be permissive, asking 'why not?' instead of 'why?''.

In conclusion, incidental findings are a major concern throughout diagnostic medicine. Developing guidelines, as is often done, might help. But overall the best way to deal with incidental findings is probably try to avoid finding them.

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Netherlands
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ORIGINAL ARTICLE

# Incidentally detected diffuse signal alterations of bone marrow on MRI: is bone marrow biopsy indicated?

**J. Spierings[1], A.N. van der Linden[2], P.H.M. Kuijper[3], L.W. Tick[1], M.R. Nijziel[1]***

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## ABSTRACT

Background: Advanced imaging techniques as magnetic resonance imaging (MRI) are increasingly performed in the diagnostic workup of patients. Incidentally, diffuse signal alterations of the bone marrow are detected because MRI visualises various components of the bone marrow. The clinical significance of these signal alterations is unknown.
Objective: The main goal of this study was to determine the diagnostic value of a bone marrow biopsy in patients with incidentally found diffuse signal alterations of the bone marrow.
Methods: We retrospectively examined all bone marrow biopsies performed from 1 January 2007 to 31 December 2013 (n = 1947). Patients were included when the biopsy was obtained following an MRI with a diffuse abnormal bone marrow signal. Patients who underwent MRI for suspected malignancy were excluded. Histological and cytological results of the bone marrow examinations were analysed.
Results: 15 of the 1947 bone marrow biopsies (0.77%) were performed because of diffuse signal alterations on MRI. In seven of these 15 bone marrow biopsies (47%) a clinically important haematological disorder was found. Eight patients had a normal bone marrow evaluation.
Conclusion: Based on this retrospective study, a bone marrow examination in patients with incidentally detected diffuse signal alterations should be considered to exclude haematological pathology. Prospective studies have to be performed to further investigate the best diagnostic strategy.

## KEYWORDS

Bone marrow reconversion, bone marrow hyperplasia, diagnostic value, hematologic diseases, magnetic resonance imaging

## INTRODUCTION

Advanced imaging techniques as magnetic resonance imaging (MRI) are increasingly performed in the diagnostic workup of patients. As a consequence, unintentionally the bone marrow is also visualised on MRI. Bone marrow contains osseous trabeculae and a cellular component. This cellular component consists of haematopoietic cells (red marrow), fat tissue (yellow marrow) and reticulum cells. The difference in composition of yellow and red marrow, the latter containing more water and less fat, explains the appearance of the bone marrow on MRI. Changes in this composition can thus be noticed and might be the first sign of disease.[1-3] Incidental abnormalities in signal intensity of the bone marrow are frequently observed in routine imaging. Several patterns of marrow change are recognised, including marrow depletion, infiltration and replacement. Another important change in distribution is the reconversion from fatty to cellular marrow.[4,5]
Throughout childhood, a physiological conversion from haematopoietic to fatty marrow is seen. This conversion occurs in a predictable pattern ending in the proximal humeral and femoral metaphyses in early adulthood.[6-9] Bone marrow reconversion, when yellow marrow is replaced with active red marrow, also known as haematopoietic hyperplasia, could be noticed in several conditions, such as anaemia and marrow replacement disorders. Smoking, obesity, obstructive sleep apnoea syndrome and endurance sports are also identified as factors that are associated with reconversion.[10-15]
The clinical significance of incidentally detected signal alterations of the bone marrow on MRI is unknown. There are no studies available on the diagnostic value of modern MRI for the detection of haematological diseases and there is a growing need for data to develop guidelines. The main goal of this study was therefore to determine the

diagnostic value of a bone marrow examination in patients with incidentally found diffuse signal alterations on MRI. Furthermore, we aimed to define a diagnostic strategy for patients with these incidental abnormal findings of the bone marrow on MRI.

## MATERIAL AND METHODS

We retrospectively identified all patients who underwent a bone marrow examination in Maxima Medical Center Eindhoven/Veldhoven, a large teaching hospital in the south of the Netherlands, from 1 January 2007 to 31 December 2013. The files of all these patients were examined. Patients were included when the bone marrow examination was obtained following an MRI with an abnormal bone marrow signal. All MRIs were performed because of musculoskeletal symptoms. There was no clinical suspicion of a haematological disorder. An abnormal bone marrow signal on MRI was defined by the radiologist and included complete and diffuse reconversion of the yellow bone marrow to haematopoietic (red) bone marrow, haematopoietic hyperplasia, recognised by a diffusely T1-weighted hypointense signal and a hyperintense signal relative to muscle on short inversion time inversion recovery and fat-suppressed T2-weighted images.[16] Patients who underwent MRI for a suspected malignancy and patients with a known haematological disorder or malignancy were excluded. All bone marrow examinations were performed within two months after the MRI. At the same time the following laboratory tests were done: erythrocyte sedimentation rare (ESR), C-reactive protein (CRP), haemoglobin, leucocytes, differentiation and platelets. Histological and cytological results of the bone marrow biopsy were analysed.

## RESULTS

### Characteristics of the study population

From 1 January 2007 to 31 December 2013, a total of 1947 bone marrow examinations were obtained. In 20 patients the biopsy was performed after detection of an abnormal bone marrow signal on MRI. Five patients were excluded because the indication for the preceding MRI was a suspected malignant disease (*figure 1*). Fifteen patients (0.77%) were included for further analysis (*table 1*). Of these 15 patients, eight were male (53%). The median age was 51.6 years (range 22-76). Thirteen patients were Caucasian (87%). The MRIs performed were of the spine, shoulder, knee and pelvis. In 12 patients (80%) abnormalities in the peripheral blood were seen.

**Figure 1.** *Flow chart of patient inclusion*

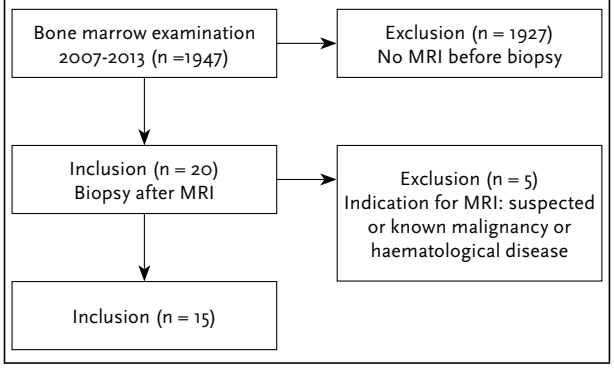


**Table 1.** *Patient characteristics*

| **Patient characteristics (n = 15)** | |
|---|---|
| Age – years<br>Median (range) | 48 (22 to 76) |
| Male sex – no. (%) | 8 (53) |
| Caucasian – no. (%) | 13 (87) |
| MRI – no. (%)<br>Spine<br>Shoulder<br>Pelvis<br>Knee | <br>10 (67)<br>2 (13)<br>2 (13)<br>1 (7) |
| Abnormal peripheral blood – no. (%) | 12 (80) |
| BMI – kg/m$^2$<br>Median (range) | <br>26.7 (19.6-29.9) |
| Smoking – no. (%) | 4 (26) |

### Prevalence of haematological disorders

In seven patients (47%) clinically significant haematological disorders were found. One patient was diagnosed with acute myeloid leukaemia (AML), one with myelodysplastic syndrome, one with multiple myeloma, one with monoclonal gammopathy of unknown significance, one with essential thrombocytosis (ET), one with classical Hodgkin's lymphoma and one with congenital spherocytosis. In every case, the diagnostic criteria formulated by the World Health Organisation were met. Eight patients had normal bone marrow histology and cytology. No differences in characteristics were observed between the patients with or without a haematological disorder (*table 2*). In the laboratory tests in patients with no haematological disorder, six patients had a mild leukocytosis, leukopenia, thrombopenia, thrombocytosis, target cells or anaemia. In the patients with a haematological disorder, in six patients a mildly increased ESR and leukopenia (patient with AML), a mild

**Table 2.** *Patient characteristics, with haematological disorders and with normal bone marrow*

| | Haematological disorder | Normal bone marrow |
|---|---|---|
| Total patients – no. (%) | 7 (47) | 8 (53) |
| Age – years<br>Median (range) | 45 (22-67) | 52 (31-76) |
| Male sex – no. (%) | 3 (43) | 5 (63) |
| Caucasian – no. (%) | 7 (100) | 6 (75) |
| BMI – kg/m²<br>Median (range) | 26.5 (19.6-28.9) | 27 (22.2-29.9) |
| Smoking – no. (%) | 2 (28) | 2 (25) |
| MRI – no. (%)<br>Spine<br>Shoulder<br>Pelvis<br>Knee | <br>3 (43)<br>1 (14)<br>2 (29)<br>1 (14) | <br>7 (87)<br>1 (13) |
| Abnormal peripheral blood – no. (%) | 6 (86) | 6 (75) |

thrombocytosis and mildly increased haematocrit (patient with ET), a mild anaemia or a mildly increased CRP (patient with Hodgkin) was found. All abnormalities found in the peripheral blood were mild and not disease specific. Statistical analysis was not performed because of the small patient population.

## DISCUSSION

This retrospective study showed haematological disorders in 47% of patients with incidentally detected diffuse signal alterations of bone marrow on MRI. Remarkably, there were no differences in baseline characteristics in the two groups, especially concerning physical examination, peripheral blood results, body weight or smoking, which could have predicted the outcome. The haematological disorders diagnosed are various and clinically relevant, requiring follow-up or medical treatment. The signal alterations of the bone marrow detected on MRI were not characteristic for any specific disease and could not distinguish between the patients with normal bone marrow and with a haematological disorder.

Although we increasingly see patients with incidentally detected diffuse signal alterations of the bone marrow on MRI in clinical practice, no recent studies are available in the literature. In 1989 Deutsch *et al.* reported ten asymptomatic patients who received a routine MRI of the knee that showed diffuse bone marrow abnormalities. Based on peripheral blood results in nine patients and bone marrow biopsy in five with a follow-up period of 4-15 months, it was concluded that the abnormalities seen on MRI were most likely benign.[17] The difference in outcome with our study can be explained in several ways. Firstly, in our study data of the bone marrow were available in all patients, in contrast with the study by Deutsch *et al.*, suggesting that haematological disorders could have been missed. Secondly, in our population more patients had an abnormal blood count, which increases the prior chance of a pathological outcome. However, we did not find any differences in ESR, haemoglobin, leucocytes, differentiation and platelets between patients with and without haematological disorders. Furthermore, the signal alterations detected in the study by Deutsch *et al.* might not be completely comparable with the signal alterations we detected, as the alterations in our patients were seen on other locations than the knee and involved modern MRI technology. Finally, our study design is different, as we started to analyse bone marrow results instead of MRI results. In this way, we were not able to allocate the patients in our hospital who might have had an abnormal signal of the bone marrow on MRI, but were not referred to a haematologist or internist. As a large part of the group had an abnormal blood count, this too might have been decisive for the physician to perform a bone marrow examination. Therefore, a selection bias in our study increases the pre-test probability of finding haematological abnormalities. The real incidence of haematological disorders will be lower than 47%. However, of all 1927 other patients who underwent bone marrow examination in the study period, not a single patient had a previous MRI examination with signal alterations of the bone marrow. To decrease the risk of any selection bias, a prospective study should be performed. The value of MRI is increasingly investigated in patients with haematological disorders. MRI is very sensitive in the staging of lymphoma patients, but it still requires bone marrow biopsy, although positron emission tomography scan might replace bone marrow biopsy for staging in the near future. In early stage myeloma and monoclonal gammopathy of unknown significance, findings on MRI correlate with earlier onset of more aggressive disease, especially using dynamic MRI techniques.[18-21] Early detection of bone marrow abnormalities might be important for determining treatment strategies and improvement of prognosis and outcome.

## CONCLUSION

In conclusion, 47% of patients with incidentally detected diffuse signal alterations of bone marrow on MRI were diagnosed with a haematological disorder. Although physical examination and laboratory tests did

not discriminate between patients with and without haematological diseases, a thorough physical examination and blood tests might increase the pre-odds likelihood before a painful bone marrow biopsy is performed. Until data of prospective studies are available, a bone marrow examination in patients with incidentally detected diffuse signal alterations should be considered to exclude haematological pathology.

## ACKNOWLEDGMENT

The results of this study were presented at the Annual Meeting of the Netherlands Association of Internal Medicine, in Maastricht, the Netherlands, on the 25 April 2013.

## DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

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ORIGINAL ARTICLE

# Endorsement of ICMJE's Clinical Trial Registration Policy: a survey among journal editors

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## ABSTRACT

Background: Since 2005, the International Committee of Medical Journal Editors (ICMJE) requires researchers to prospectively register their clinical trials in a publicly accessible trial registry. The Consolidated Standards of Reporting Trials (CONSORT) statement has supported this policy since 2010. We aimed to evaluate to what extent biomedical journals have incorporated ICMJE's clinical trial registration policy into their editorial and peer review process.

Methods: We searched journals' instructions to authors and performed an internet survey among all journals publishing reports of randomised controlled trials that follow ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (n = 695), and/or that endorse the CONSORT statement (n = 404) accessed in January 2011. Survey invitations were sent to the email addresses of the editorial offices and/or editors-in-chief of included journals in June 2011.

Results: For 757 ICMJE and/or CONSORT journals, we identified that they published RCT reports. We could assess the instructions to authors of 747 of these; 384 (51%) included a statement of requiring trial registration, and 33 (4%) recommended this. We invited 692 editorial offices for our survey; 253 (37%) responded, of which 50% indicated that trial registration was required; 18% cross-checked submitted papers against registered records to identify discrepancies; 67% would consider retrospectively registered studies for publication. Survey responses and specifications in instructions to authors were often discordant.

Conclusion: At least half of the responding journals did not adhere to ICMJE's trial registration policy. Registration should be further promoted among authors, editors and peer reviewers.

## KEYWORDS

Outcome reporting bias, publication bias, trial registration

## INTRODUCTION

Clinical trials provide essential evidence on the effectiveness and safety of healthcare interventions. Unfortunately, many studies remain unpublished and results are often presented selectively in trial reports.[1] Since positive and favourable results are more likely to get published than negative and inconclusive ones,[2] the medical literature and systematic reviews are at risk of bias, with an overrepresentation of promising results and an underrepresentation of adverse effects.[3-5]

In response to accumulating evidence of selective publication and reporting in the biomedical literature, the International Committee of Medical Journal Editors (ICMJE) introduced a policy in 2005 that requires researchers to register their clinical trial in a publicly accessible trial registry before the enrolment of the first patient, in order to be considered for publication.[6,7] Trial registration improves access to clinical trial data, allows the easy identification of unpublished studies by clinicians, researchers and reviewers,[8-11] and provides journal editors and peer reviewers with the opportunity to discover and prevent selective reporting of results. Since 2010, ICMJE's trial registration policy is also supported by the Consolidated Standards of Reporting Trials (CONSORT) Statement.[12,13]

Although the number of registered trials has grown explosively since 2005,[14] it is unknown how well journals currently adhere to ICMJE's registration policy and whether they consider publication of unregistered or retrospectively registered trials, cross-check submitted papers against registered data, and manage discrepancies between the two. We aimed to evaluate to what extent journals that announced to follow ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals[15] and journals that endorse the CONSORT statement, have incorporated trial registration into their editorial and peer review process. For this aim we examined their instructions to authors and performed a survey distributed to the editorial offices of these journals.

## MATERIALS AND METHODS

### Identification of journals

In January 2011, all journals following ICMJE's recommendations (ICMJE journals; member list obtained at http://icmje.org/journals.html) and/or endorsing the CONSORT statement (CONSORT journals; list of adopting journals obtained at http://www.consort-statement.org/about-consort/consort-endorsement/consort-endorsers---journals/) were identified, along with their webpages, and the email addresses of their editorial offices and editors-in-chief. If the latter information was not provided, we tried to identify it through the Google search engine.

To find out whether these journals publish reports of randomised controlled trials (RCTs), one author scanned their webpages and published issues. Journals that did not publish RCTs and journals for which we were unable to obtain this information were excluded. The RCT publication status of each journal was confirmed by a second reviewer, with discrepancies being resolved through discussion. If necessary, a third party made the final decision. Included journals were subdivided into general and speciality journals.

### Instructions to authors

Between January and September 2011, one author extracted data from the instructions to authors of included journals (*table 1*). Here we excluded journals without a webpage and journals that only provided instructions to authors in languages other than English. All extracted data were confirmed by a second reviewer. Here, also, discrepancies were resolved through discussion, if necessary with a third party. We assessed whether the journal made a statement about endorsement of ICMJE's or CONSORT's recommendations, and whether a link to these guidelines was provided. We categorised such links as webpages (providing an internet-link to a web address containing the recommendations of either two), suitable references (providing a reference to an article describing ICMJE's criteria published in or after 2004, or to an article describing CONSORT's criteria published in or after 2001), or obsolete references (providing a reference to an ICMJE article published before 2004, or a CONSORT article published before 2001). In addition, we checked whether

**Table 1.** *Information provided in the instructions to authors of ICMJE and CONSORT journals*

| | All journals (n = 747) | Journals on ICMJE list only (n = 366) | Journals on CONSORT list only (n = 271) | Journals on both lists (n = 110) |
|---|---|---|---|---|
| Statement about following ICMJE's recommendations | 542 (73%) | 253 (69%) | 197 (73%) | 92 (84%) |
| Statement about following CONSORT's recommendations | 408 (55%) | 95 (26%) | 230 (85%) | 83 (76%) |
| | | | | |
| Statement about policy regarding trial registration | 417 (56%) | 153 (42%) | 191 (71%) | 73 (66%) |
| Registration: required | 384 (51%) | 137 (37%) | 181 (67%) | 66 (60%) |
| Registration: recommended | 33 (4%) | 16 (4%) | 10 (4%) | 7 (6%) |
| Registration: no notification of registration policy | 330 (44%) | 213 (58%) | 80 (30%) | 37 (34%) |
| Reference to specific trial registry provided | 261 (35%) | 62 (17%) | 149 (55%) | 50 (46%) |

the instructions to authors contained a statement about the journal's policy regarding trial registration and, if so, whether registration was required or recommended, and whether specific trial registries were suggested.

**Survey among editors**

For the survey among editors, we excluded journals for which we were unable to identify an email address. Some editorial offices manage more than one journal. When the contact information of such journals overlapped, we considered these journals as a single potential survey responder.

In July 2011, included journals were invited to participate in our online survey through an email to the editorial office. When this email address was not available or not working, we sent the invitation to the journal's editor-in-chief. Two reminders were sent out, each a month apart. We used SurveyMonkey software (www.surveymonkey.com) to collect responses, which was open until November 2011.

The survey consisted of eight multiple choice questions, some with an option to further clarify chosen answers. One question addressed the respondent's function within the journal's editorial staff; the other questions addressed the journal's policy regarding trial registration and to what extent this policy was incorporated into the editorial and peer review process (*table 2*).

**Analysis**

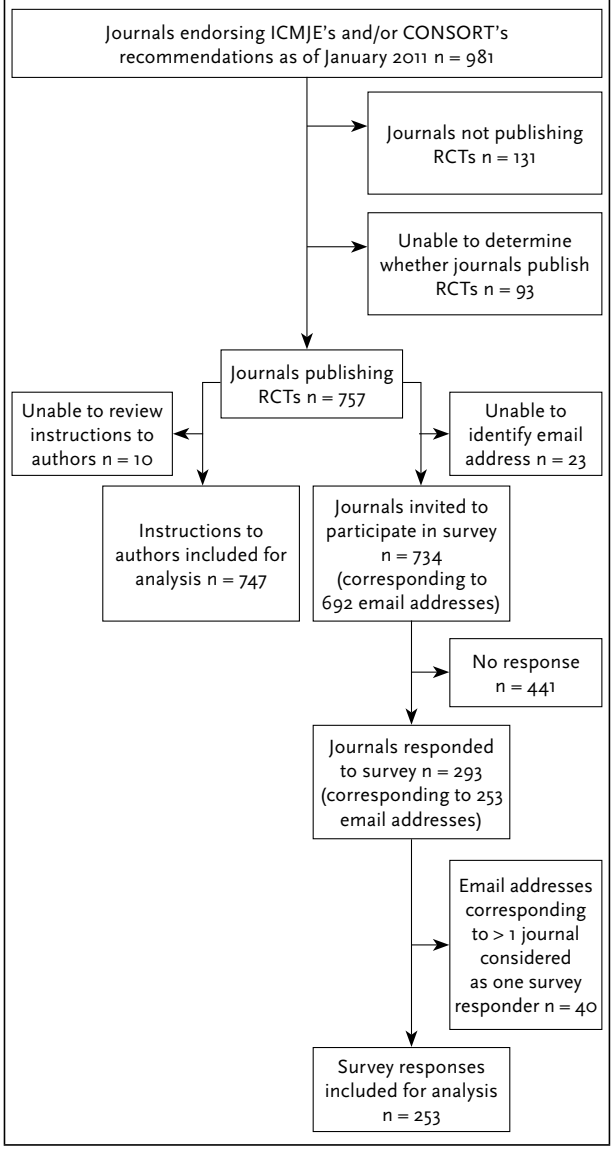
Data are reported as frequencies and percentages. Incomplete surveys were included in the analysis, for which all available responses were used. Chi-squared test statistics were used to evaluate differences between ICMJE journals and CONSORT journals, between general and speciality journals, and between higher and lower impact journals. For this last analysis, we categorised journal impact factors into quartiles. When a journal had no impact factor, it was categorised in the lowest quartile. When a single person responded on behalf of several journals, we took the average of the impact factors for these journals.

P-values of 0.05 or less were considered statistically significant. Data were analysed using SPSS version 22.0.

## RESULTS

In January 2011, there were 695 ICMJE journals and 404 CONSORT journals. Of these, 118 journals were on both lists. We excluded 224 journals because they did not publish RCTs (n = 131), or because we were unable to obtain this information (n = 93) (*figure 1*). The final study sample consisted of 757 journals: 69 (9%) were general journals, and 688 (91%) were speciality journals.

**Figure 1.** *Flowchart of ICMJE and CONSORT journals through the study*




**Results from examination of instructions to authors**

Since we were unable to assess the instructions to authors of ten journals, due to language restrictions (n = 6) or because a website was lacking (n = 4), we included 747 journals in this analysis (*figure 1*). Data extracted from the instructions to authors are provided in *table 1*.

Of the ICMJE journals, 345 (73%) made a statement about following ICMJE's recommendations. Of these, 291 provided a link to ICMJE's webpage, 15 provided a suitable reference (published after 2004) containing ICMJE's recommendations, and 26 provided a reference to an obsolete publication. Of the CONSORT journals, 313 (82%) made a statement about endorsement of the CONSORT statement. Of these, 280 provided a link to CONSORT's

**Table 2.** *Summary of responses to survey among ICMJE and CONSORT journals*

| | All responding journals | Journals on ICMJE-list only | Journals on CONSORT-list only | Journals on both lists |
|---|---|---|---|---|
| *What is your journal's policy regarding registration of clinical trials?* | | | | |
| Total number of respondents | 232 | 119 | 79 | 34 |
| Registration required | 117 (50%) | 60 (50%) | 35 (44%) | 22 (65%) |
| Registration recommended | 57 (25%) | 26 (22%) | 24 (30%) | 7 (21%) |
| Not (yet) implemented | 58 (25%) | 33 (28%) | 20 (25%) | 5 (15%) |
| *What is your journal's policy regarding registration of observational studies?* | | | | |
| Total number of respondents | 232 | 119 | 79 | 34 |
| Registration required | 19 (8%) | 13 (11%) | 4 (5%) | 2 (6%) |
| Registration recommended | 76 (33%) | 37 (31%) | 21 (27%) | 18 (53%) |
| Registration not necessary | 137 (59%) | 69 (58%) | 54 (68%) | 14 (41%) |
| *Is the ICMJE's clinical trial registration policy included in your journal's 'Instructions to Authors' section?* | | | | |
| Total number of respondents | 226 | 115 | 77 | 34 |
| Yes | 142 (63%) | 72 (63%) | 44 (57%) | 26 (77%) |
| No | 84 (37%) | 43 (37%) | 33 (43%) | 8 (24%) |
| *Is the ICMJE's clinical trial registration policy incorporated into your editorial and peer review processes?* | | | | |
| Total number of respondents | 216 | 110 | 73 | 33 |
| Yes | 99 (46%) | 41 (37%) | 35 (48%) | 23 (70%) |
| No | 117 (54%) | 69 (63%) | 38 (52%) | 10 (30%) |
| *For submitted manuscripts, does your journal cross-check the reported data in the manuscript against the prospectively registered data?* | | | | |
| Total number of respondents | 206 | 103 | 70 | 33 |
| Yes | 37 (18%) | 16 (16%) | 12 (17%) | 9 (27%) |
| No | 169 (82%) | 87 (85%) | 58 (83%) | 24 (73%) |
| *What do you do when discrepancies are found between the reported data in the manuscript and the prospectively registered data?* | | | | |
| Total number of respondents* | 34 | 16 | 9 | 9 |
| We do not act on that | 5 (15%) | 2 (13%) | 1 (11%) | 2 (22%) |
| Discrepancies are resolved between authors and editors | 29 (85%) | 14 (88%) | 8 (89%) | 7 (78%) |
| *Does your journal consider manuscripts for publication when the underlying trial has been registered after enrolment of the first patient?* | | | | |
| Total number of respondents | 202 | 101 | 69 | 32 |
| Yes | 103 (51%) | 54 (54%) | 34 (49%) | 15 (47%) |
| Yes, under certain conditions | 33 (16%) | 13 (13%) | 11 (16%) | 9 (28%) |
| No | 66 (33%) | 34 (34%) | 24 (35%) | 8 (25%) |

***Only journals that had answered 'Yes' to the previous question (indicating that they cross-checked reported and registered data) were included in the analysis of this question.**

webpage, eight provided a suitable reference (published after 2001) containing CONSORT's recommendations, and ten provided an obsolete reference.

ICMJE member journals stated significantly less often on their webpage that they required trial registration (37%) than journals that had adopted CONSORT only (67%), or journals that had adopted both (60%, $p < 0.0001$). No significant difference was found between the proportion of general journals mentioning that trial registration was required (42%), compared with speciality journals (52%, $p = 0.12$).

Specific trial registries that were recommended by journals making a statement about requiring or recommending trial registration were most often ClinicalTrials.gov

(n = 116), International Standard Randomised Controlled Trial Number register (n = 81), the Australian New Zealand Clinical Trial Register (n = 59), or the Netherlands Trial Register (n = 55).

**Results from survey**

We were unable to identify an email address of the editorial office and/or editor-in-chief for 23 of the 757 included journals (*figure 1*). Some email addresses corresponded to two journals (n = 2), three journals (n = 1), or 39 journals (n = 1). We sent the invitation to 692 email addresses and between June and November 2011, 253 (37%) of these responded, including 51 partially completed surveys.

The following persons participated in the survey: 140 (55%) editors-in-chief, 52 (21%) managing editors, 24 (10%) editors or associate editors, 18 (7%) administrators, and 19 (8%) other types of employees. We found no evidence of selective response: 35% of the journals that made no notification on trial registration in their instructions to authors responded to the survey, compared with 38% of the journals that required registration, and 40% of the journals that recommended registration. This difference was not significant (p = 0.67).

Answers to specific questions are provided in *table 2*. Only 50% (95% CI: 45-56%) of the respondents indicated that their journal required trial registration. Significantly more journals with an impact factor in the upper quartile (above 3.5) required registration (76%) than those in the lower three quartiles (42%, 38% and 46%, p < 0.0001). There were no significant differences in trial registration requirement between ICMJE journals, CONSORT journals, and journals that had adopted both (50%, 44% and 65%, p = 0.14), nor between general and speciality journals (55% and 50%, p = 0.60). Less than one-fifth of the respondents, and 22% of the journals requiring trial registration, cross-checked the reported data in the manuscript against the registered data. Journals that cross-checked the data did not always act in case of discrepancies.

Two-thirds of all the responding journals, and 56% of the journals that indicated to require trial registration also considered study reports for publication when the underlying trial was registered after enrolment of the first patient.

**Discrepancies between instructions to authors and survey responses**

Journals' trial registration policies as indicated in the survey and specifications in the instructions to authors were often not concordant (*table 3*). For a quarter of the journals that responded that trial registration was required, we were unable to find a corresponding statement on registration in the instructions to authors.

We were also unable to find a statement on trial registration in the instructions to authors of 25% of the journals that indicated that such a statement was available. In contrast, we found a statement on trial registration for 28% of the journals that had responded that such a policy was not included in their instructions to authors. Such discrepancies were found in 37% of the journals with an impact factor in the lowest quartile, compared with 29%, 20% and 19% in those in the higher three quartiles (p = 0.11).

**Table 3.** *Concordance between journals' registration policies as defined in the instructions to authors and according to survey responders*

| **Registration policy as found in instructions to authors:** | **Registration policy according to survey responder** | | |
|---|---|---|---|
| | Required (n = 115) | Recommended (n = 57) | Not implemented (n = 57) |
| Required (n = 118) | 87 (76%) | 17 (30%) | 14 (25%) |
| Recommended (n = 12) | 3 (3%) | 7 (12%) | 2 (4%) |
| No notification on registration policy (n = 99) | 25 (22%) | 33 (58%) | 41 (72%) |

## DISCUSSION

Although the ICMJE has required prospective trial registration since 2005 and CONSORT has supported this policy since 2010, at least half of the journals following ICMJE's Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and/or endorsing the CONSORT statement do not adhere to this registration policy.

Only half of the journals responding to our survey indicated that trial registration was required. Two-thirds considered trials for publication that were registered after study initiation, against the ICMJE recommendation about prospective registration. These findings are in line with the results of previous studies, which have shown that about half of the published RCTs are registered after study completion, or are not registered at all.[16-20]

Four-fifths of the responding journals in our analysis did not cross-check submitted papers against registered records, even when requiring trial registration. This provides authors with the opportunity to publish their results selectively. A number of studies have shown that this happens frequently. Discrepancies between registered and published outcomes have been found in up to half of published trial reports.[8,16,18,19,21] A survey among peer reviewers showed that only one-third of them compared submitted manuscripts with registered trial information and reported any discrepancies to the journal editors.[22] These results indicate that it is still fairly easy for authors to

get around the ICMJE's trial registration requirement and to publish unregistered and improperly registered studies. We found that half of the journals indicated in their instructions to authors that trial registration was required. Another recent evaluation scrutinised the instructions to authors for a random selection of 200 biomedical journals publishing clinical trial reports. The authors concluded, based on information on journals' webpages, that only 28% required registration.[23]

In our study, journals' registration policies were frequently absent from webpages and information provided in the survey sometimes differed from the instructions to authors. It seems that survey responders were not always aware of the content of the instructions to authors of their own journals; this applied to a quarter of the journals indicating that they required trial registration and to a quarter of the journals without a registration policy. Citations referring to ICMJE's or CONSORT's recommendations were often lacking or obsolete in adopting journals. Similar deficiencies in instructions to authors have been found in previous studies. An evaluation of author guidelines of 167 medical journals in 2003 showed that a quarter of those mentioning CONSORT and more than half of those mentioning ICMJE provided obsolete references.[24] In another analysis, a survey was sent to journal editors about endorsement of the CONSORT statement. The study authors observed that a positive response about mentioning CONSORT in instructions to authors could not be confirmed in a quarter of cases.[25]

In 2010, *BMJ* and *The Lancet* both published a statement in which they indicated that, from then on, they would strongly recommend authors to also register observational research.[26,27] Although this policy led to some controversy in the biomedical literature,[28,29] our survey indicates that more than a quarter of the ICMJE and/or CONSORT journals currently recommend registration of observational research, and a minority even requires it.

A number of elements in our analysis deserve consideration. The response rate to our survey was only 37%, and we cannot exclude selective participation. Although response rates did not significantly differ between journals that indicated in their instructions to authors that trial registration was required and those that did not, it is conceivable that journals without an active implementation of ICMJE's registration policy felt less motivated to participate. If this is the case, we may have even overestimated adherence to ICMJE's policy. We had to exclude 93 journals because we were uncertain whether they published RCT reports, mostly due to language restrictions. Data extraction, performed by a single author, was confirmed by a second one, but we may have missed information regarding registration policies in instructions to authors.

Our study was performed six years after ICMJE's trial registration policy was introduced, which should have given journals enough time to incorporate the policy into their instructions to authors, and into their editorial and peer review process. Our survey did not address reasons for not yet complying with ICMJE's policy. Future studies should focus on the question why many ICMJE and CONSORT journals currently do not follow these requirements, and which steps should be taken before they are willing to apply them into their editorial and peer review process. This way, barriers can be identified and potential solutions can be developed.

Selective reporting and non-publication of research findings lead to a waste of valuable research efforts and compromise the reliability of the biomedical literature.[30] There have been many examples in which the effectiveness of healthcare interventions was overestimated when solely based on published results. How can we expect medical practitioners to adequately perform evidence-based medicine when the published literature is strongly biased by positive findings? We observe a tendency towards more transparency in health research, and initiatives such as CONSORT and ICMJE's trial registration policy represent important examples. These initiatives have led to undisputable improvements: the quality of reporting has visibly increased,[31] and the number of registered trials and national trial registries has grown substantially over the past decade. Unfortunately, adoption tends to go slowly. There is still a long way to go before the scientific community can fully profit from the potential benefits of trial registration. Journal editors and peer reviewers – especially those supporting ICMJE's and/or CONSORT's recommendations – should be further encouraged to require prospective registration from each clinical trial that is presented to or reported in their journal.

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## DISCLOSURES

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ORIGINAL ARTICLE

# Accurate and fast diagnostic algorithm for febrile urinary tract infections in humans

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## ABSTRACT

Background: The urine dipstick that detects nitrite and leukocyte esterase, and urine sediment is commonly used to diagnose or exclude urinary tract infections (UTIs) as the source of infection in febrile patients admitted to the emergency department of Dutch hospitals. However, the diagnostic accuracy of the urine dipstick and urine sediment has never been studied in this specific situation.

Methods: Urinary samples of 104 febrile consecutive patients were examined. Urine culture with ≥ $10^5$ colonies/ml of one or two known uropathogen was used as the gold standard. The diagnostic value of the urine dipstick, urine sediment and Gram stain at various cut-off points was determined and used to develop a new diagnostic algorithm. This algorithm was validated in a new group of sepsis patients based on systemic inflammatory response syndrome (SIRS) criteria.

Results: A positive nitrite on the urine dipstick (specificity 99%) rules in UTI. This is the first step of our diagnostic algorithm. The second step is to exclude UTI by absence of bacteria in the urine sediment (sensitivity 94%). The third and last step is the number of leucocytes/high-power field (hpf) in the urine sediment. Less than 10 leucocytes/hpf makes UTI unlikely whereas ≥ 10 leucocytes/hpf indicates UTI. In contrast to urine dipstick and/or urine sediment results alone, our algorithm showed both a high sensitivity (92%) and specificity (92%) and was validated in a new sepsis population.

Conclusion: Our accurate and fast diagnostic algorithm, which combines the selective results of urine dipstick and urine sediment, can be easily used to diagnose UTI in febrile patients at the emergency department of Dutch hospitals.

## KEYWORDS

Diagnostic algorithm, urinary tract infection, fever, emergency department, urine sediment, urinary dipstick, Gram stain

## INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections in humans and is a frequent cause of hospitalisation.[1] In lower UTIs such as urethritis and cystitis most patients complain of dysuria. UTIs with signs of tissue invasion (prostatitis or pyelonephritis) can be more difficult to recognise because of the absence of specific symptoms such as flank pain or abdominal pain, especially in the elderly.[2] Pyelonephritis can lead to severe sepsis or septic shock and can be life-threatening.[3,4] Early goal-directed treatment of sepsis or septic shock improves survival of patients with severe infection.[5,6] Therefore, accurate diagnostics to demonstrate or exclude UTIs in febrile patients presenting to the emergency department are very important.

The urine culture is worldwide accepted as the gold standard in diagnosing urinary tract infections.[7-9] It is the commonly used method that can provide detailed information about the pathogen and its sensitivity to different antibiotics. However, a urine culture is costly and takes at least 24-48 hours. The urine dipstick that detects nitrite and leukocyte esterase in the urine is the standard procedure to diagnose UTI in Dutch family practice (NHG standard). UTI suspicion by the patient and a positive nitrite test were the strongest indicator of an uncomplicated UTI in general practice.[10] However, the diagnostic value of the urine dipstick depends on the population in which it is used and varies widely.[11-16] Other

available tests are microscopic examination of the urine sediment and Gram stain. These are both labour intensive and therefore costly methods. The diagnostic value of the urine sediment is variable as it depends on many factors including the expertise of the analyst.[7,12,14,17] Assessing a Gram stain seems to be a more sensitive and specific and therefore a better method than assessing the urine dipstick or urine sediment.[17-20] However, the Gram stain is rarely used as a diagnostic tool in diagnosing UTI because it takes too long before the results are available.

At the emergency department of our and many other Dutch hospitals, the urine dipstick is used to diagnose or exclude UTI as the source of infection in febrile patients. However, the diagnostic value of the urine dipstick has never been studied in this specific population.[11] Therefore, we determined the diagnostic accuracy of urine dipstick and compared it with the urine sediment and Gram stain in febrile patients presenting to the emergency department of our hospital. Based on these results we developed a new algorithm to diagnose UTI fast and accurately in febrile patients admitted to the emergency department.

## MATERIAL AND METHODS

### Setting

This was a prospective cohort study, performed at the emergency department of Isala in Zwolle. Isala is one of the largest non-academic hospitals in the Netherlands. Over 5000 internal medicine patients present annually to the emergency department of Isala.

### Study population

Consecutive patients older than 18 years who were admitted to the internal medicine emergency department and had fever > 38.0 °C on admission or had fever > 38.0 °C at home on the day of presentation were included. Patients who had used antibiotics during the past 48 hours, had an indwelling catheter or had chemotherapy-induced leucocytopenia (< 4.0 x $10^9$ cells/l) at presentation were excluded. The inclusion period started on 14 December 2009 and ended on 28 March 2010 (15 weeks). The medical ethics committee of our hospital declared no objections.

### Clinical assessment

Patient characteristics were obtained from the electronic patient file. The junior doctor on duty noted the health history, current medication, symptoms of patients and physical findings in the medical record. We registered diabetes mellitus when patients were treated with glucose-lowering medications or diabetes was mentioned in the medical record. Patients with immunosuppressive therapy (i.e. prednisone or chemotherapy) were classified as immunocompromised hosts. C-reactive protein and leukocyte counts were recorded. Blood cultures where performed when indicated by the physician on duty. Whether patients had systemic inflammatory response syndrome (SIRS) was determined. SIRS was defined by the presence of at least two of the following symptoms: body temperature greater than 38.5 °C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, an arterial partial pressure or carbon dioxide less than 4.3 kPa and white blood cell count greater than 12 x $10^9$ cells/l.

### Urinalysis

The emergency department nurse collected urine and divided each sample into two containers. The first container was sent to the clinical chemistry laboratory where urine dipstick and urine sediment were performed. Laboratory professionals unaware of the other test results performed all tests according to our standard hospital protocols. The Aution MAX AX-4280® (Iris Diagnostics, Chatsworth) was used to perform the Uriflet® dipstick (ARKRAY Europe B.V, Amstelveen). Microscopic analysis of the urine sediment was performed after centrifugation of 10 ml urine at 2000 rpm for five minutes and decantation of the supernatant. A preparation was assessed and the number of leucocytes and erythrocytes (magnification 40 x 10) per high-power field (hpf) was determined. Bacteria were scored semi-quantitatively because they were too small to count.

The second container, cooled at 4 °C in the refrigerator, was sent by courier to the microbiology laboratory. Gram staining and urine culture were performed. A Gram stain was made of uncentrifuged urine. The presence of leucocytes and erythrocytes was counted at 10 x 10 magnification. The shape (cocci or rods), colour (Gram positive or Gram negative) and the number of bacteria per hpf were determined at a magnification of 100 x 10 in a semiquantitative way. *Table 1* shows possible results of the used tests.

For urine cultures, 10 µl urine was placed on two different Agars (a chromogenic agar and a sheep blood agar). These plates were incubated at 35 °C and read for growth after at least 24 hours. Isolated organisms were reported as the number of colony-forming units per millilitre (CFU/ml) urine. A specimen that grew ≥ $10^5$ CFU/ml of one or two uropathogens was defined as a positive urine culture. UTI was defined as a positive urine culture and used as the gold standard for UTI.[8,9,21]

### Discharge diagnosis

The focus for fever was based on clinical, radiological or microbiological evidence. When patients had a positive urine culture but another explanation for the fever (e.g. pneumonia), UTI was classified as a lower URI or could

**Table 1.** *Possible results of urinary dipstick, urine sediment and Gram stain*

| Test | Determination | Count | Value |
|---|---|---|---|
| Urine dipstick | Nitrite | < 0.08 mg/dl | - |
| | | > 0.08 mg/dl | + |
| | Leukocyte esterase | < 75 leu/µl | - |
| | | 75 leu/µl | + |
| | | 250 leu/µl | ++ |
| | | 500 leu/µl | +++ |
| Urine sediment | Leucocytes | < 5 /hpf | |
| | | > 5 /hpf | |
| | | > 10/hpf | |
| | | > 20 /hpf | |
| | | > 40 /hpf | |
| | Bacteria | | - |
| | | | + |
| | | | ++ |
| Gram stain | Leucocytes | 0-1 /hpf | - |
| | | 2-5 /hpf | + |
| | | 6-15 /hpf | ++ |
| | | > 15 /hpf | +++ |
| | Bacteria | 0 | - |
| | | 0-1 | trace |
| | | 2-15 | + |
| | | 16-100 | ++ |
| | | > 100 | +++ |

**Bacteria in the urine sediment were counted semi-quantitatively; hpf = high-power field.**

be due to asymptomatic bacteriuria. When UTI was the only focus for fever we diagnosed febrile UTI. Urosepsis was diagnosed in patients with febrile UTI who met SIRS criteria or had a positive blood culture with the same pathogen as the urine culture.

**Statistical analysis**

To evaluate the diagnostic value of the urine dipstick, urine sediment and Gram stain we extracted 2 x 2 tables of true-positive, false-positive, false-negative and true-negative results at various cut-off points. The urine culture was used as the gold standard for UTIs. From each of these tables we computed sensitivity, specificity, positive predictive value and negative predictive value. Furthermore positive and negative likelihood ratios (LR+ and LR-) and the diagnostic odds ratio (DOR) had been calculated:

LR+ = Sensitivity/ (1-specificity)
LR- = (1-sensitivity)/ specificity
DOR = LR+/ LR-

A LR+ above 10 or a LR- below < 0.1 are considered to provide strong evidence to rule in or rule out diagnoses respectively. The highest DOR has the highest diagnostic accuracy.

**Diagnostic algorithm and validation study**

Based on our results we developed a diagnostic algorithm in which we combined different results of urine dipstick and urine sediment with high sensitivity or specificity. The diagnostic value of our diagnostic algorithm was calculated. To confirm the diagnostic value of our algorithm a validation study was performed in a new sepsis population. Sepsis patients are a clearly defined group that is easily recognised in the emergency department and an important clinical group of severely ill patients. In addition, not all septic patients are febrile, for example elderly patients. Therefore we validated our algorithm in a new group of septic patients. All patients presenting to the emergency department with at least two SIRS criteria and complete data were included between 1 January 2011 and 31 December 2011. We used the same exclusion criteria as the original population and performed the same set of tests as mentioned above. We calculated the diagnostic values of our proposed diagnostic algorithm.

## RESULTS

In the inclusion period 181 presentations because of fever were seen at the emergency department (*table 2*). Twenty-seven patients were not included because of incomplete data or incorrect inclusion. Fifty patients were excluded because of the following reasons: chemotherapy-induced leucocytopenia at admission (n = 13), use of antibiotics in the past 48 hours (n = 37) and/ or use of indwelling catheters (n = 14). The results of the remaining 104 patients were analysed. The patient characteristics are shown in *table 2*.

The study population included more males (58%) than females; 60 patients (58%) were diagnosed with SIRS. The median temperature at presentation was 38.7 °C (IQR 38.4-39.5 °C) and the median C-reactive protein value was 60 mg/ml (IQR 15-168 mg/ml).

Of the 97 blood cultures performed, 23 were positive. A total of 31% of the patients (32/104) had a positive urine culture with 34 pathogens. All calculations were done using this group (n = 32). *E. coli* was most often cultured (22 times, 69%). Three patients had a possible other focus of infection and were diagnosed with lower UTI or asymptomatic bacteriuria. Nineteen out of 29 patients with febrile UTI had urosepsis defined as positive blood culture

**Table 2.** *Patient characteristics of febrile patients presented to the emergency department (n = 104)*

| | N | % |
|---|---|---|
| Gender | | |
| Male | 60 | 57.7 |
| Female | 44 | 42.3 |
| Diabetes mellitus | 24 | 23.1 |
| Immunocompromised host | 26 | 25.0 |
| SIRS at admission | 60 | 57.7 |
| | **Median** | **Interquartile range** |
| Age (years) | 62 | 49-78 |
| Temperature (°C) | 38.7 | 38.4-39.5 |
| CRP (mg/l) | 60 | 15-168 |
| Leukocyte count ( x $10^3$/$mm^3$) | 11.2 | 8-14.5 |

**CRP = C-reactive protein; SIRS = systemic inflammatory response syndrome.**

(8 patients) or ≥ 2 SIRS criteria. Of the 29 patients with febrile UTI only seven patients (24%) had dysuria of which two patients had dysuria and flank pain. Six patients had flank pain without dysuria (21%).

**Evaluation of tests**

The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and the diagnostic odds ratio of the different tests are summarised in *table 3* (urine sediment and urine dipstick) and *table 4* (Gram stain).

*Urine dipstick results*

The sensitivity of a positive nitrite was very low (28%) but its specificity was very high (99%). Leukocyte esterase 1+ had a sensitivity of only 75% and a specificity of 86%. At leukocyte esterase 3+, the sensitivity was 59% and the specificity 94%. The combination of nitrite (first diagnostic step) and leukocyte esterase (second diagnostic step) resulted in a sensitivity of 75% at leukocyte esterase 2+ and only 66% at leukocyte esterase 3+.

*Urine sediment results*

The sensitivity and negative predictive value of bacteria in the urine sediment were very high: both 96%. In contrast, the specificity and positive predictive value were low: 47% and 50%, respectively.

The sensitivity and negative predictive value of leucocytes/hpf in the urine sediment was comparable with the leukocyte esterase detected by the urine dipstick (77% and 87%) but the specificity was higher. Raising the cut-off point to ≥ 10 leucocytes/hpf did not reduce the sensitivity but increased the specificity to 94%. Therefore, this is the best cut-off point. At the cut-off point ≥ 40 leucocytes/hpf, the specificity and positive predictive value were 100%.

*Gram stain results*

The presence of bacteria in the Gram stain had a high sensitivity and negative predictive value: 94% and 97% respectively. At bacteria 2+ and 3+, the specificity (93-99%), positive predictive value (85-94%) and positive likelihood ratio (12.6-55.6) were also high. Diagnostic values of leucocytes were lower than for bacteria in the Gram stain.

**Table 3.** *Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio and diagnostic odds ratio of urinary dipstick and urine sediment at various cut-off points in febrile patients admitted to the emergency department*

| Test | Determination | Cut-off point | Sens | Spec | PPV | NPV | LR + | LR- | DOR |
|---|---|---|---|---|---|---|---|---|---|
| Urine dipstick | Nitrite | 1+ | 28% | 99% | 90% | 76% | 20.3 | 0.73 | 27.8 |
| | LE | 1+ | 75% | 86% | 71% | 89% | 5.4 | 0.29 | 18.6 |
| | | 2+ | 69% | 92% | 79% | 87% | 8.3 | 0.34 | 24.2 |
| | | 3+ | 59% | 94% | 83% | 84% | 10.7 | 0.43 | 24.8 |
| Urine sediment | Bacteria | 1+ | 96% | 47% | 50% | 96% | 1.8 | 0.08 | 22.0 |
| | | 2+ | 65% | 81% | 65% | 81% | 3.4 | 0.43 | 8.0 |
| | Leukocytes | > 5 | 77% | 85% | 74% | 87% | 5.2 | 0.27 | 19.0 |
| | | > 10 | 77% | 94% | 87% | 88% | 12.1 | 0.25 | 48.9 |
| | | > 20 | 69% | 96% | 90% | 85% | 16.3 | 0.32 | 50.6 |
| | | > 40 | 46% | 100% | 100% | 77% | ∞ | 0.54 | ∞ |

**LE = leucocyte esterase; sens =sensitivity; spec = specificity, PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; DOR = diagnostic odds ratio.**

**Table 4.** *Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio and diagnostic odds ratio of the gram Stain at various cut-off points in febrile patients admitted to the emergency department*

| Test | Determination | Cut-off point | Sens | Spec | PPV | NPV | LR+ | LR- | DOR |
|---|---|---|---|---|---|---|---|---|---|
| Gram stain | Bacteria | 1+ | 94% | 81% | 68% | 97% | 4.8 | 0.08 | 62.1 |
| | | 2+ | 88% | 93% | 85% | 94% | 12.6 | 0.13 | 93.8 |
| | | 3+ | 77% | 99% | 94% | 93% | 55.6 | 0.23 | 241.4 |
| | Leukocytes | 1+ | 88% | 75% | 61% | 93% | 3.5 | 0.17 | 21.0 |
| | | 2+ | 63% | 88% | 69% | 84% | 5.0 | 0.43 | 11.7 |
| | | 3+ | 47% | 96% | 83% | 80% | 11.3 | 0.55 | 20.3 |

**Sens = sensitivity; spec = specificity, PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; DOR = diagnostic odds ratio.**

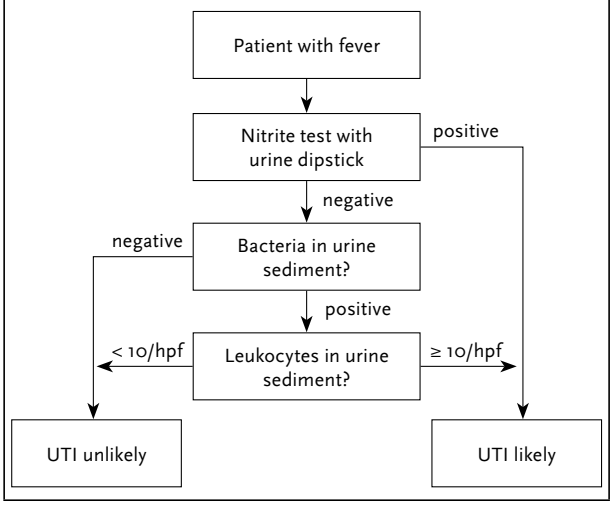
*Diagnostic algorithm*

Based on our results of urine dipstick and urine sediment we developed a new diagnostic algorithm as shown in *figure 1*. The first diagnostic step is the nitrite test with high specificity to rule in UTI when positive. When nitrite is negative, a UTI can be ruled out by the absence of bacteria in the urine sediment. A UTI is likely if bacteria and ≥ 10 leucocytes/hpf are present in the sediment, while when less than 10 leucocytes/hpf are present UTI is unlikely. The sensitivity of this strategy is 92%, the negative predictive value 96%, the specificity 92% and the positive predictive value 85%. The diagnostic odds ratio was very high at 128.

*Validation of our diagnostic algorithm*

During the validation study period 94 patients who met our sepsis protocol criteria were included in the study and 33 patients were excluded. Of the 61 analysed patients, 22 patients had a UTI. The diagnostic algorithm had a sensitivity of 73%, specificity 100% (no false-positive results). This resulted in an infinite positive likelihood ratio and diagnostic odds ratio. This relative low sensitivity is caused by six false-negative results. Analysis of these results showed that five out of six patients had a positive urine culture but with another focus of fever. Almost all (16 out of 17) clinically relevant UTIs were detected when using our diagnostic algorithm with a very high specificity and positive predictive value.

**Figure 1.** *New diagnostic algorithm for febrile urinary tract infections in patients admitted to the emergency department*




## DISCUSSION

The results of our study show that selective combining of urine dipstick and urine sediment has very high diagnostic accuracy in diagnosing UTI in febrile patients admitted to the emergency department. To our knowledge a diagnostic algorithm for diagnosing febrile UTI has never been described before. Most guidelines for febrile UTI or complicated UTI concentrate on the treatment of febrile UTI. In our opinion, before goal-directed empirical antibiotic treatment can be given, an accurate diagnostic procedure should first be performed.

The urine dipstick had limited diagnostic value in diagnosing febrile UTI in our study population. Only a positive nitrite indicates UTI because of the high specificity of the test, as previously reported.[11,13] Therefore, a positive nitrite was incorporated as the first step in our diagnostic algorithm. The sensitivity of nitrite was surprisingly low (28%). Earlier studies showed higher sensitivities of 40-57%.[11,22] This difference can be explained because we did not collect early morning urine, but examined urine on presentation to the emergency department, usually during the day or at night. Gram-negative bacteria containing nitrate reductase has to be in the bladder for at least four hours to convert nitrate into nitrite. In addition, not all Gram-negative bacteria contain nitrate reductase. The leukocyte esterase

test, the other diagnostic test of the urine dipstick, did not contribute significantly to the diagnostic process in our study population. A negative leukocyte esterase reaction cannot exclude UTI and only 3+ leucocytes/hpf indicate UTI. This corresponds with previous studies that showed very variable sensitivity (48-86%) and specificity (17-93%) for this test.[11,13,22] The presence of bacteria in the urine sediment had a high sensitivity, thus absence of bacteria excludes UTI with high accuracy. Therefore, we selected the absence of bacteria as the second step in our diagnostic algorithm. The specificity of leucocytes/hpf in the urine sediment appeared to be higher than the leukocyte esterase reaction of the urine dipstick while sensitivity is equal. The third and last step of our diagnostic algorithm includes < 10 leucocytes/hpf to exclude and ≥ 10 leucocytes/hpf to indicate UTI. Our diagnostic algorithm had both a high sensitivity (92%) and specificity (92%) and is clearly superior to the individual urine dipstick and urine sediment tests. Also, the combination of the nitrite and leukocyte esterase reaction of the urine dipstick at 2+ or 3+ has a much lower sensitivity (75 and 66% respectively) and will miss a significant number of UTIs. Therefore, our algorithm is based on tests with either high sensitivity or specificity in order to exclude or include UTI with high accuracy. It is necessary to perform both diagnostics (urine sediment and urine dipstick) in clinical practice when using our fast and accurate diagnostic algorithm.

Our diagnostic algorithm (*figure 1*) was validated in a new sepsis population. The specificity and positive predictive value were even higher than in the original study due to the absence of false-positive results. Applying the diagnostic algorithm in this population predicted febrile UTI very accurately and missed only one clinically relevant UTI. Therefore, our diagnostic algorithm will help to improve the diagnostic procedure and can be easily used in daily practice in the management of febrile and septic patients in the emergency department of Dutch hospitals.

Demonstration of bacteria in the Gram stain had the highest sensitivity and specificity. This has previously been reported both in adult patients[17] and children[18]. The higher sensitivity and specificity of the Gram stain for the demonstration of bacteria are due to the fact that stained bacteria are better visible at microscopic examination. However, Gram staining takes much more time and is not available 24 hours/day in the emergency department of Dutch hospitals. In addition, our diagnostic algorithm is a much quicker alternative to the Gram stain with almost equal diagnostic value. Possibly new quick techniques, such as flow cytometry, which could automatically quantify the number of bacteria in urine will be a good alternative for examining a Gram-stained urine preparation.

We selected fever as the major inclusion criterion because most admissions to the emergency department in the Netherlands are due to fever without an evident focus.[23] Our study shows that specific signs of a complicated UTI such as dysuria and flank pain are only present in a selection of patients with febrile UTI, as reported before.[24] We only excluded patients with an indwelling catheter (almost always positive culture), use of antibiotics (negative urinary culture despite UTI) and leucocytopenia (possible absence of leucocyturia despite UTI), because this negatively influences the diagnostic values. Earlier studies excluded patients with diabetes, immunodeficiency disorders or patients who were unable to provide a reliable history.[12] Because a large proportion of the internal medicine patient population do have these comorbidities (*table 2*), we choose to include these patients in our study. We conclude that our inclusion and exclusion criteria represent a significant and clinically important population that is frequently admitted to the emergency department.

A limitation of our study is the relatively small number of patients. A larger study population could give more reliable study results. We excluded patients on antibiotics during the past 48 hours, with an indwelling catheter or with leucocytopenia on presentation. This means that our diagnostic algorithm cannot be used in these patient populations. A positive nitrite would still indicate UTI in leucocytopenic patients. When nitrite is negative we advise to assess a Gram stain for the presence of bacteria. To our knowledge there are no good methods to diagnose UTI when antibiotics are used before admission. The urine culture would be only positive if the uropathogen is resistant to the given antibiotic. In about 30% of febrile UTI patients the positive blood culture can be used to diagnose complicated UTI even when patients used antibiotics before admission.[25] Symptomatic UTI and asymptomatic bacteriuria in the urine of patients with and without an indwelling catheter cannot be distinguished with today's technics. According to the IDSA guideline the most reliable urine culture can be obtained from urine of a newly inserted indwelling catheter after removal of the previous colonised catheter.[26]

In conclusion, with the use of our diagnostic algorithm febrile UTI can be diagnosed much faster and easier in daily practice. When febrile UTI is diagnosed, early and goal-directed antibiotic therapy can be started, which will improve survival of patients with urosepsis.

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## DISCLOSURES

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ORIGINAL ARTICLE

# Patients at risk for contrast-induced nephropathy and mid-term effects after contrast administration: a prospective cohort study

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## ABSTRACT

Objectives: Determine the incidence of patients at risk for contrast-induced nephropathy (CIN), the incidence of CIN and mid-term effects (renal replacement therapy/death < one month) to measure the impact of CIN in a general patient population undergoing intravenous contrast-enhanced computed tomography (CECT).

Methods: We conducted a prospective study in consecutive patients undergoing intravenous CECT from October 2012 to May 2013. Data were obtained through scripted interviews and the electronic patient records. Presence of risk factors and kidney function before and after CECT and the follow-up for one month were evaluated.

Results: We included 998 patients (mean age: 60 years). Estimated GFR was ≥ 60 ml/mg/1.72 $m^2$ in 886 (88.8%) patients, 30-59 ml/mg/1.72 $m^2$ in 108 (10.8%) patients and < 30 ml/min/1.73 $m^2$ in 4 (0.4%) patients. We found diabetes mellitus in 137 (13.7%), anaemia in 70 (7.0%), congestive heart failure in 92 (9.2%), peripheral arterial disease in 34 (3.4%), age > 75 years in 126 (12.6%) patients and 301 (30.2%) used nephrotoxic medication. Fifty-eight (5.8%) patients were at risk for CIN; 35 (60.3%) risk patients received intravenous prophylactic hydration. Of the hydrated patients, 11 underwent follow-up within one week; of the non-hydrated patients seven underwent follow-up within one week. Two (2/58: 3.4%) patients developed CIN (increased serum creatinine ≥ 44 μmol/l or ≥ 25%); there was no difference between hydrated and non-hydrated patients (1/35:1/23). The incidence of renal replacement therapy and death within one month was zero for both.

Conclusion: The number of patients at risk is low. CIN incidence is low, even in patients not receiving prophylactic hydration. No patients received renal replacement therapy or died. The impact of CIN is low. Extensive CIN prevention guidelines seem superfluous.

## KEYWORDS

Acute kidney injury, computed tomography, contrast medium, prevention, risk factors

## INTRODUCTION

Contrast-induced nephropathy (CIN) is considered to be the most serious complication following intravascular contrast medium administration. It is defined by an increase in serum creatinine of ≥ 44 μmol/l or ≥ 25% within 24-72 hours after contrast medium administration.[1-3] CIN is associated with increased morbidity (usually defined as the need for renal replacement therapy) and mortality.[4]

To reduce CIN incidence, national CIN prevention guidelines have been introduced.[5,6] These state that patients with chronic kidney disease indicated by an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 $m^2$ in combination with other risk factors are at risk for CIN.[5,6] To enable prevention all patients receiving intravascular iodinated contrast medium should be screened to find those at risk.[5,6] Prevention measures for patients at risk entail discontinuation of diuretics and nephrotoxic medication in addition to prophylactic intravenous hydration before and after contrast-enhanced procedures. See *table 1* for more details on patients at risk.

**Table 1.** *Patients at risk for CIN according to CIN prevention guidelines*

| | |
|---|---|
| **Patients at risk for CIN** | |
| 1. | Multiple myeloma or Waldenström's disease with light chain proteinuria |
| 2. | eGFR 30-44 ml/min/1.73 m² |
| 3. | eGFR 45-59 ml/min/1.73 m² and diabetes mellitus |
| 4. | eGFR 45-59 ml/min/1.73 m² and ≥ 2 other risk factors (not diabetes mellitus) |
| **Other risk factors** | |
| 1. | Anaemia (haematocrit male: 0.39 l/l and female: 0.36 l/l) |
| 2. | Congestive heart failure |
| 3. | Peripheral vascular disease |
| 4. | Age > 75 years |
| 5. | Use of nephrotoxic medication/ diuretics (e.g. NSAIDs) |
| 6. | Dehydration |
| 7. | Symptomatic hypertension |
| 8. | Contrast administration within < 24 hours |

Most iodinated contrast medium administration takes place during intravenous contrast-enhanced computed tomography (CECT).[7] This patient population differs from the patient population undergoing cardiac intervention from which data for CIN prevention guidelines were obtained.[5,6] In CIN prevention guidelines a CIN incidence up to 35% is mentioned.[5,6] In addition, an incidence of up to 45% of renal replacement therapy and death following contrast-enhanced procedures in patients who developed CIN is mentioned in these guidelines.[5,6] In contrast to this patient population, the incidence of CIN following intravenous CECT, as established in two meta-analyses analyses, is low: 4.96% (95% CI: 3.79-6.47) and 6.4% (95% CI: 5.0-8.1) respectively.[8,9] The incidence of mid-term effects following intravenous CECT is suggested to be low to non-existent.[10]

The effort and costs that have to be made to detect patients at risk for CIN and subsequently apply prevention measures seems to be disproportional considering the low CIN incidence and the probability that there are no mid-term effects following CIN.[10-12] These facts have led to discussion about the need for such extensive prevention programs in terms of feasibility, patient benefit and costs.[13-17]

To our knowledge there are no studies evaluating the incidence of patients at risk for CIN, the incidence of CIN, need for renal replacement therapy and death in a sizable number of consecutive patients undergoing intravenous CECT. If we have this overview of the real impact and consequences (mid-term effects) of CIN on a general patient population undergoing intravenous CECT, we could provide some clarity in the discussion on the necessity and extensiveness of the current CIN prevention guidelines in these patients. Therefore, we describe the following findings in a general patient population undergoing intravenous CECT:

1. The incidence of patients at risk for CIN.
2. The incidence of CIN defined as an increase in serum creatinine of ≥ 44 μmol/l or ≥ 25% within seven days after intravenous CECT.
3. The incidence of renal replacement therapy or death within one month after intravenous CECT.

## MATERIALS AND METHODS

### Study design and setting

We conducted a prospective cohort study at the Academic Medical Center, University of Amsterdam from October 2012 to May 2013. The data obtained from this patient population were published previously in an article regarding screening strategies in the context of CIN prevention and another article concerning costs related to screening strategies was recently accepted for publication.[11,12] Informed consent was waived by the hospital's medical ethics committee because the study was non-invasive and patient burden during participation in this study was considered to be negligible.

### Study population

We included consecutive patients scheduled to undergo intravenous CECT. Exclusion criteria were: patients aged < 18 years and patients who were admitted to the emergency department or the intensive care unit because most CIN prevention guidelines describe separate prevention strategies for these patients.[5,6] Patients were also excluded if they did not wish to participate; they did not speak Dutch or English and came without a translator; were not approachable due to logistical reasons or their data were incompletely entered in the database.

Patients received either Iopromide (Ultravist 300, Bayer, Leverkusen, Germany), or Iomeprol (Iomeron 400, Bracco, Milan, Italy) during the intravenous CECT. Both are low-osmolar and non-ionic contrast media.

### Data collection and measurements

Data were collected by scripted interviews using a questionnaire and from the hospital's electronic patient record. The patients were interviewed on the day of the intravenous CECT. The interviews were conducted by four researchers, three medical students and one research fellow (SM, GN, RW, DV), all instructed to conduct the interview in an uniform manner according to the questionnaire.

*Baseline characteristics:* Demographic data (age, sex, length, weight, Afro-European) and type and indication

for intravenous CECT were collected. Body mass index (BMI) was calculated based on height and weight (kg/m$^2$).

*Kidney function:* From the electronic patient records we collected information on kidney function (i.e. eGFR, serum creatinine) before the intravenous CECT. The eGFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula. We corrected the eGFR for the Afro-Europeans (black people) by multiplying the outcome by 1.20, in accordance with the MDRD formula. eGFR was known in all patients as indicated by the national guideline used in our hospital.[5] This means that in general this was measured < 12 months prior to the intravenous CECT. However, in case of known kidney disease or a clinically relevant event (e.g. cardiovascular event, use of nephrotoxic medication) which could have influenced kidney function and took place in the past 12 months, kidney function was measured after the event. We also registered the time interval between baseline eGFR measurement and intravenous CECT.

*Risk factors:* We assessed the presence of risk factors for CIN. During the interview patients were asked whether or not they suffered from diabetes mellitus and (congestive) heart failure. We checked the electronic patient record to verify the presence of the above-mentioned risk factors. In addition, we checked the electronic patient record to see if patients had anaemia, peripheral arterial disease, if patients used diuretics/ nephrotoxic drugs (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides) and if patients were diagnosed with either multiple myeloma or Waldenström's disease with light chain proteinuria.
Patients were considered to be anaemic if they had a haematocrit < 0.39 l/l (males) or < 0.36 l/l (females) in accordance with the World Health Organisation definition of anaemia and in accordance with national CIN prevention guidelines.[5,6] We considered medication to be nephrotoxic if this was mentioned in the national database containing information on all (human) registered drugs in the Netherlands and Europe.[18]
Other risk factors such as dehydration, symptomatic hypotension and contrast administration within < 24 hours are mentioned in the guidelines, but were not assessed as we were not able to objectively determine dehydration and symptomatic hypotension during the interview or in the electronic patient record. Another risk factor described in the CIN prevention guideline is contrast administration within < 24 hours before intravenous CECT. This was not applicable as these patients underwent elective intravenous CECT.

*CIN prophylaxis:* We also used the questionnaire to assess whether or not patients were instructed to increase oral fluid intake, discontinue potential nephrotoxic medication/ metformin or received prophylactic intravenous hydration in accordance with the hospital CIN prevention protocol. That protocol indicates that patients who need prophylactic intravenous hydration should receive 0.9% sodium chloride (NaCl), 3-4 ml/kg/h for four hours before and after intravenous CECT. In patients with severe kidney disease or congestive heart failure administration of 1 ml/kg/h for 12 hours is recommended before and after intravenous CECT. The final decision to actually apply prevention measures in patients at risk was left to the discretion of the treating physician.

**Incidence of patients at risk for CIN**

From the above-mentioned data we were able to assess how many patients fit the profile of patients at risk for CIN. We considered the following patients to be at risk for CIN: 1) Patients with multiple myeloma or Waldenström's disease with light chain proteinuria; 2) Patients with an eGFR 30-44 ml/min/1.73 m$^2$; 3) Patients with an eGFR 45-59 ml/min/1.73 m$^2$ and diabetes mellitus; 4) Patients with an eGFR 45-59 ml/min/1.73 m$^2$ and ≥ two other risk factors (anaemia; congestive heart failure; peripheral vascular disease; age > 75 years; use of nephrotoxic medication (e.g. NSAIDs) and diuretics. See also *table 1* for an overview of patients at risk for CIN. We calculated the incidence of patients at risk for CIN by dividing the number of at-risk patients by the total number of patients included in the cohort study.

**Follow-up for CIN incidence and mid-term effects**

CIN incidence: Serum creatinine levels were checked before and after intravenous CECT. By comparing the levels of serum creatinine before and after administration of intravenous CECT, we determined whether CIN occurred. We defined CIN as an increase of serum creatinine ≥ 44 µmol/l or ≥ 25% within seven days. We considered this time interval to be acceptable to determine CIN, as the time interval for CIN determination of 24-72 hours, mentioned in the literature, is not feasible in daily clinical practice due to weekends and holidays.
Mid-term effects: For the mid-term events we assessed the outcomes death and need for renal replacement therapy within one month in patients at risk for CIN.

*Statistical analysis*

Normally distributed variables were reported as means ± standard deviation (SD) and categorical variables as numbers and percentages. Data were statistically analysed using SPSS 20® (SPSS20 Inc., Chicago, IL, USA). Differences between groups were assessed by $\chi^2$ test or Fisher's exact test. A two-sided p-value of < 0.05 was used as an indicator for statistical significant differences.

We used Excel and Access (Microsoft Office® 2003 for Windows XP) to organise the obtained data.

## RESULTS

### Patient population

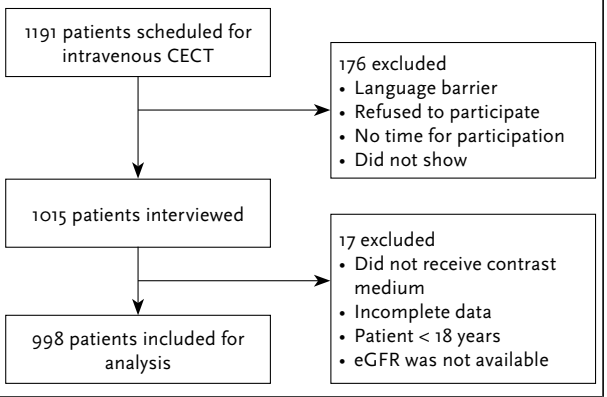
Between October 2012 and May 2013 there were 1191 eligible patients. Of these patients, 176 could not be interviewed due to a language barrier, or the patients did not want to participate, there was no time to interview the patient or the patient did not show up for the examination. We finally interviewed 1015 patients. Seven patients did not receive intravenous iodinated contrast medium during their computed tomography; for another six patients the data could not be used for analysis due to incomplete data, one patient was < 18 years and in three of these patients the eGFR was missing. We finally included 998 patients for analysis. See *figure 1* for more information on eligible, interviewed and included patients.

### Patient characteristics

We included 545 (54.6%) males and 453 (45.4%) females with a mean age of 59.94 years ± 13.56 (SD), 57 patients (5.7%) with Afro-European ethnicity, a mean height of 173 cm ± 10 (SD), a mean weight of 76 kg ± 16 (SD) and a mean BMI of 25 kg/m² ± 5 (SD).

We included 886 (88.8%) patients with an eGFR ≥ 60 ml/mg/1.72 m². There were 108 (10.8%) patients with an eGFR between 30-59 ml/mg/1.72 m² (chronic kidney disease stages 3A and 3B) and 4 (0.4%) with an eGFR < 30 ml/min/1.73 m² (stage 4). Most intravenous CECT examinations were related to malignancy (n = 708, 70.9%), concerned intravenous CECT of the chest and abdomen (n = 387, 38.8%) and were performed in outpatients (n = 925, 92.7%). See details in *table 2*.

**Figure 1.** *Patient inclusion flowchart*




**CECT = contrast-enhanced computed tomography; eGFR = estimated glomerular filtration rate.**

### Kidney function (estimated serum creatinine and glomerular filtration rate at baseline)

The mean baseline serum creatinine was 79 µmol/l ± 23 (SD) in all patients, 74 µmol/l ± 16 (SD) in the patients with an eGFR ≥ 60 ml/mg/1.73 m², 115 µmol/l ± 23 (SD) in patients with an eGFR between 30-59 ml/mg/1.73 m², and 225 µmol/l ± 49 (SD) in patients with eGFR < 30 ml/min/1.73 m².

The exact eGFR was only available in patients with eGFR < 60 ml/min/1.73 m² (mean: 49 ± 9 (SD)), as in patients with an eGFR ≥ 60 ml/min/1.73 m² the absolute value of eGFR is not registered in our electronic patient record/laboratory results. The mean eGFR was 50 ml/min/1.73 m² ± 8 (SD) in patients with an eGFR between 30-59 ml/mg/1.73 m² and 22 ml/min/1.73 m² ± 4 (SD) in the patients with an eGFR < 30 ml/mg/1.73 m². See *table 3* for details on baseline kidney function.

In the majority of the patients (646/998, 64.7%) eGFR was measured within one month before intravenous CECT. In 201 patients, eGFR was measured between 1-3 months before intravenous CECT, and in 146 patients this was between 3-12 months. In five patients the exact time between eGFR measurement and the intravenous CECT was unknown as patients were referred from other institutions. See *table 3* for more details.

### Risk factors and preventive measures

Diabetes mellitus was present in 137 (13.7%) patients. Seventy (7.0%) had anaemia at the time of the intravenous CECT, 92 (9.2%) suffered from congestive heart failure, 34 (3.4%) had peripheral arterial disease, 126 (12.6%) of the patients were older than 75 years and 301 (30.2%) of the patients used nephrotoxic medication or diuretics.

In total 145 (14.5%) patients indicated that they had received information to increase oral fluid intake on the day before and the day of the intravenous CECT and 132 (13.2%) actually increased their oral fluid intake as a result of this. Twenty-one patients indicated that they were advised to discontinue medication on the day before and the day of the intravenous CECT and 22 patients indicated that they stopped taking their medication. One patient had stopped all medication on his own initiative because he thought this would be beneficiary for the intravenous CECT. In total 60 patients received prophylactic intravenous hydration, including eight patients with an eGFR ≥ 60 ml/min/1.73 m². Data are presented in *table 3*.

### Patients at risk for CIN

Of the 108 patients with eGFR 30-59 ml/min/1.73 m², 56 patients were eventually identified as at risk for CIN: one patient with multiple myeloma or Waldenström's disease, 26 patients with an eGFR between 30-44 ml/min/1.73 m², 15 patients with an eGFR between 45-59 ml/min/1.73 m² + diabetes mellitus and 14 patients with eGFR between 45-59 ml/min/1.73 m² and two risk factors (comprising anaemia,

**Table 2.** *Patient characteristics*

| | Total study population (n = 998) | eGFR ≥ 60 ml/min/1.73 m² (n = 886) | eGFR 30-59 ml/min/1.73 m² (n =108) | eGFR <30 ml/min/1.73 m² (n = 4) |
|---|---|---|---|---|
| *Baseline characteristics* | | | | |
| Male: female n (%) | 545 (54.6%):453 (45.4%) | 487 (55.5%):399 (45.5%) | 57 (52.8%):51 (47.2%) | 1 (25.0%):3 (75%) |
| Afro-European n (%) | 57 (5.7%) | 48 (5.4%) | 9 (8.3%) | 0 (0%) |
| Age (years) mean ± SD | 60 (14) | 59 (14) | 66 (12) | 63 (20) |
| Height (cm) mean ± SD[a] | 172 (10)[a] | 173 (10) | 17 (9) | 173 (13) |
| Weight (kg) mean ± SD | 76 (16) | 76 (16) | 80 (19) | 72 (8) |
| BMI (kg/m²) mean ± SD[a] | 25 (5)[a] | 25 (5) | 27 (5) | 24 (3) |
| *Type of CT scan* | | | | |
| Chest/ Abdomen n (%) | 387 (38.8%) | 339 (38.3%) | 48 (44.4%) | 0 |
| Abdomen n (%) | 146 (14.6%) | 131 (14.8%) | 14 (13.0%) | 1 (25.0%) |
| Kidney n (%) | 107 (10.7%) | 89 (10.0%) | 17 (15.7%) | 1 (25.0%) |
| Pancreas n (%) | 95 (9.5%) | 90 (10.2%) | 5 (4.6%) | 0 |
| Cardiac n (%) | 56 (5.6%) | 49 (5.5%) | 6 (5.6%) | 1 (25.0%) |
| Chest n (%) | 53 (5.3%) | 51 (5.8%) | 2 (1.9%) | 0 |
| Aorta n (%) | 45 (4.5%) | 39 (4.4%) | 5 (4.6%) | 1 (25.0%) |
| Liver n (%) | 39 (3.9%) | 33 (3.7%) | 6 (5.6%) | 0 |
| Cerebrum n (%) | 12 (1.2%) | 12 (1.4%) | 0 (0.0%) | 0 |
| Other n (%) | 58 (5.8%) | 53 (6.0%) | 5 (4.6%) | 0 |
| *Indication for CT scan* | | | | |
| Malignancy n (%) | 448 (44.9%) | 393 (44.4) | 55 (50.9%) | 0 |
| Suspected malignancy n (%) | 260 (26.1%) | 233 (26.3) | 27 (25.0%) | 0 |
| Vascular deformation n (%) | 79 (7.9%) | 70 (7.9) | 8 (7.4%) | 1 (25.0%) |
| Nephrological disease n (%) | 34 (3.4%) | 29 (3.3) | 5 (4.6%) | 0 |
| Infection n (%) | 51 (5.1%) | 51 (5.8) | 0 | 0 |
| Kidney donation n (%) | 15 (1.5%) | 15 (1.7) | 0 | 0 |
| Family history of cardiac disease n (%) | 13 (1.3%) | 12 (1.4) | 1 (0.9%) | 0 |
| Pulmonary embolism n (%) | 7 (0.7%) | 5 (0.6) | 2 (1.9%) | 0 |
| Macroscopic anaemia n (%) | 6 (0.6%) | 3 (0.3) | 2 (1.9%) | 1 (25.0%) |
| Cysts (liver, kidney, pancreas) n (%) | 7 (0.7%) | 7 (0.8) | 0 | 0 |
| Angina pectoris n (%) | 9 (0.9%) | 8 (0.9) | 1 (0.9%) | 0 |
| Other n (%) | 69 (6.9%) | 60 (6.8) | 7 (6.5%) | 2 (50.0%) |
| *Patient status* | | | | |
| Inpatient n (%) | 73 (7.3%) | 55 (6.2%) | 17 (15.7%) | 1 (25.0%) |
| Outpatient n (%) | 925 (92.7%) | 831 (93.8%) | 91 (84.3%) | 3 (75.0%) |

[a] **n = 997, one patient did not know his or her height.**

congestive heart failure, peripheral arterial disease, age > 75 years, use of nephrotoxic medication). The remaining 52 patients with an eGFR 45-59 ml/min/1.73 m² (19 with one risk factor and 33 with no risk factors) were not considered to be at risk for CIN, therefore no follow-up data were registered.

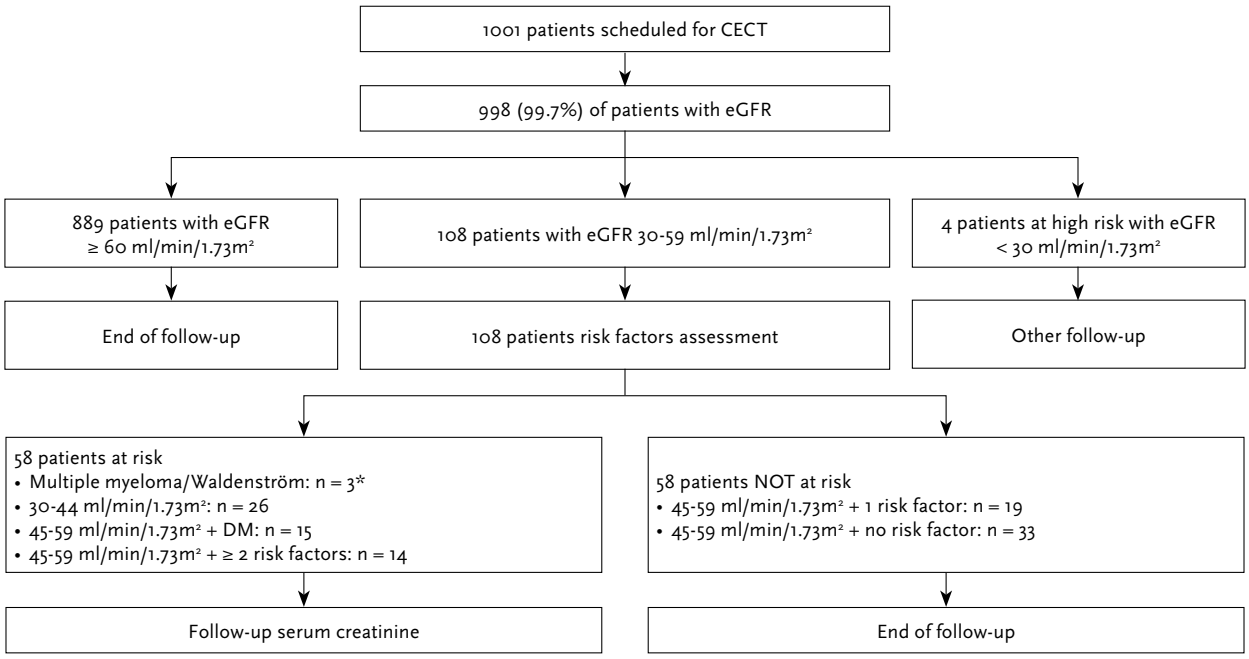
In the group of patients with eGFR ≥ 60 ml/min/1.73 m², two patients with multiple myeloma or Waldenström's disease were also considered to be at risk for CIN. The total number of patients at risk for CIN was 58 patients (5.8%). See details in *figure 2*.

**Table 3.** *Kidney function and other risk factors*

| | Total study population (n = 998) | eGFR ≥ 60 ml/min/1.73 m² (n = 886) | eGFR 30-59 ml/min/1.73 m² (n =108) | eGFR < 30 ml/min/1.73 m² (n = 4) |
|---|---|---|---|---|
| *Kidney function* | | | | |
| Serum creatinine (µmol/l) mean ± SD[a] (number of patients in which data were available) | 80 ± 23 a | 74 ± 16 (n = 863) | 115 ± 23 (n = 106) | 225 ± 49 (n = 4) |
| eGFR (ml/min/1.73 m²) mean ± SD[b] | | - | 50 ± 8b | 22 ± 4 |
| *Risk factors associated with our guidelines[c]* | | | | |
| Diabetes mellitus n (%) | 137 (13.7%) | 112 (12.6%) | 25 (23.1%) | 0 |
| Anaemia n (%) | 70 (7.0%) | 56 (6.3%) | 13 912.0%) | 1 (25.0%) |
| Congestive heart failure n (%) | 92 (9.2%) | 76 (8.6%) | 16 (14.8%) | 0 |
| Peripheral vascular disease n (%) | 34 (3.4%) | 25 (2.8%) | 9 (8.3%) | 0 |
| Age > 75 years n (%) | 126 (12.6%) | 95 (10.7%) | 30 (27.8%) | 1 (25.0%) |
| Use of nephrotoxic medication n (%) | 301 (30.2) | 254 (28.7%) | 45 (41.7%) | 2 (50.0%) |
| Multiple myeloma or Waldenström's disease n (%) | 3 (0.3%) | 2 (0.2%) | 1 (0.1%) | |
| *Preventive measures* | | | | |
| Oral fluid intake advised n (%)/ followed advice n (%) | 145 (14.5%)/ 132 (13.2%) | 118 (13.3%)/107 (12.1%) | 26 (24.1%)/25 (23.1%) | 1 (25.0%)/0 (0.0%) |
| Discontinue medication advice n (%)/stopped medication n (%) | 21 (2.1%)/22 [d]92.2%) | 16 (1.8%)/ 16(1.8%) | 4 (3.7%)/ 5[d] (4.6) | 1 (25.0%)/ 1 (25.0%) |
| Prophylactic intravenous hydration n (%) | 60 (6.0%) | 8 (0.9%) | 50 (46.3%) | 2 (50.0%) |

**[a]Serum creatinine values were missing in 25 patients; [b]absolute eGFR was missing in 3 patients; [c]other three risk factors: hydration, symptomatic hypertension and contrast administration within < 24 hours were not assessed; [d] One patient had stopped all medication on own initiative thinking this would be beneficiary for the intravenous iodinated contrast enhanced examination.**

**Figure 2.** *Defining patients at risk*




*** Two of these patients had an eGFR ≥ 60 ml/min/1.73 m²; CECT = contrast-enhanced computed tomography; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate.**

**Prevention regimen in patients at risk**

Of the 58 patients at risk for CIN, 35 underwent prophylactic intravenous hydration and the remaining 23 patients did not receive prophylactic intravenous hydration. Patients with multiple myeloma or Waldenström's disease were equally distributed between patients who received prophylactic intravenous hydration and patients not receiving prophylactic intravenous hydration (1/35 vs 2/23; p = 0.556). The number of patients with an eGFR 30-44 ml/min/1.73 m² were also equally distributed (19/35 vs 7/23; p = 0.074) between patients who received prophylactic intravenous hydration and patients who did not. The same applies for patients with an eGFR between 45-59 ml/min/1.73 m² + diabetes mellitus (8/35 vs 7/23; p = 0.519) and for patients with an eGFR between 45-59 ml/min/1.73 m² + ≥ 2 risk factors: 7/35 vs 7/23; p = 0.364. See details in *figure 3*.

**Incidence of CIN**

Of the 35 at-risk patients who received prophylactic intravenous hydration, 11 patients had a follow-up serum creatinine measurement within seven days. Of the 23 at-risk patients who did not receive prophylactic intravenous hydration, seven patients underwent serum creatinine follow-up within seven days. In total two patients had CIN (2/58 patients at risk for CIN: 3.4%, 2/18 11.1%). When taking into account the total number of screened patients, the incidence of CIN was 0.2% (2/998). Data on further serum creatinine follow-up were not available.

The distribution of the number of patients with CIN between patients who received prophylactic intravenous hydration and patients who did not receive prophylactic intravenous hydration was comparable (1/35 vs 1/23; p = 0.761). See *figure 3*.

**Mid-term follow-up of patients at risk**

None of the 58 patients at risk for CIN received renal replacement therapy or died within one month after intravenous CECT (see also *figure 3*).

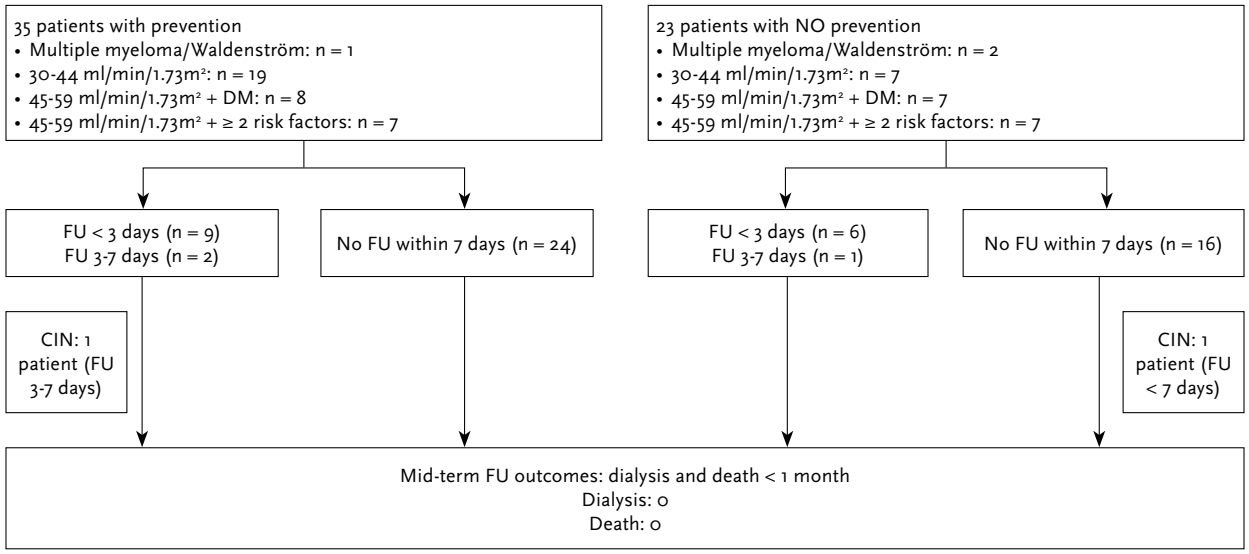
## SUMMARY AND CONCLUSIONS

**Summary**

Firstly, our study showed that the number of patients at risk for CIN in a general population undergoing intravenous CECT is low (5.8%), even in a population with a high prevalence of relevant risk factors (66.8%). Secondly, the CIN incidence was low to very low. In the group of patients at risk for CIN, the CIN incidence was 3.4% (2/58) and in the total group of screened patients this was 0.2% (2/998). Prophylactic intravenous hydration does not seem to influence CIN incidence. Thirdly, mid-term effects following intravenous CECT were non-existent.

When we consider the patients at risk for CIN we found that almost all patients defined as being at risk had eGFR 30-59 ml/min/1.73 m² (10.8% of the patient population (108/998)). In a study by Liu *et al.* a higher number (31/171, 18.2%) of patients were seen with an eGFR 30-59 ml/min/1.73 m², but the number of patients at risk for CIN was also low: 10 patients (5.8%) would be categorised as at risk, which is comparable to our patient population.[19] Recent updates of international CIN prevention guidelines

**Figure 3.** *Follow-up serum creatinine and mid-term follow-up of 58 patients at risk*




**DM = diabetes mellitus; FU = follow-up.**

indicate that prevention measures are only indicated in patients with an eGFR < 45 or 40 ml/min/1.73 m² in combination with risk factors for CIN.[20,21] In addition, a recent study by Davenport *et al.* comparing patients who did and did not undergo intravenous CECT showed no significant difference in CIN or acute nephropathy incidence in patients with an eGFR ≥ 30 ml/min/1.73 m² (odds ratio: 2.96 (95% CI: 1.22-7.17).[22] If we were only to consider patients with an eGFR < 45 or < 30 ml/min/1.73 m² this would decrease the incidence of patients at risk in our patient population to 3.0% or 0.4% (30 or 4/998), respectively.

The low CIN incidence in our patient population is in accordance with two meta-analyses performed on CIN incidence, which mostly contained patients at risk for CIN (overall pooled CIN incidences were 4.96% (95% CI: 3.79-6.47) and 6.4% (95% CI: 5.0-8.1)).[8,9] In our study not all patients at risk received prevention measures; this might be a reflection of the fact that clinicians do not always consider CIN to be clinically relevant because they seldom or never experience mid-term effects. In addition (inter)national surveys show that the majority of clinicians and radiologists do not know exactly which patients belong to the at risk category and what the appropriate steps would be in this case.[23,24] These factors could reduce compliance. The fact that the distribution of CIN incidence was equal between patients who did and did not receive prophylactic intravenous hydration before and after intravenous CECT could imply that this prevention measure is not as effective as has been assumed up to now. This is confirmed in studies were a high number of patients did not receive prophylactic intravenous hydration: 348/493 (70.6%) and 577/663 (87.0%).[4,25] Here there was no difference in CIN incidence between patients who did and did not receive prophylactic intravenous hydration (3.2 vs 1.4% calculated Fisher's exact test, p = 0.363).

Finally, this paper showed incidences of 0% for the need for renal replacement therapy and for death. Mid-term effects following intravenous CECT were also assessed in a systematic review and meta-analysis by McDonald *et al.*[26] They analysed the difference in need for renal replacement therapy and death following intravenous CECT comparing patients undergoing intravenous CECT with patients undergoing unenhanced procedures in an effort to see if there is causality between intravenous CECT and acute nephropathy and these mid-term effects.[26] The pooled RRs for need of renal replacement therapy and occurrence of death were 0.88 (95%: CI 0.23-3.43; p = 0.85) and 0.95 (95% CI: 0.55-1.67; p = 0.87), respectively, when comparing the two groups.[26] In the group of patients undergoing intravenous CECT, the number of patients needing renal replacement therapy was 24/7270 (0.33%) compared with 0% in our population and death was 178/7359 (2.0%) compared with 0% in our population.[26] However, the follow-up period for these outcomes in the studies included in the review by McDonald was defined as three months,[27] or as the duration of hospitalisation,[28,29] or was not defined at all.[30,31] This could have led to overestimation or underestimation of the incidence of these mid-term effects. Another limitation of their study is that they did not take into account the use of prophylactic intravenous hydration.

**Limitations**

This study was performed in an academic hospital and most of the intravenous CECT examinations were related to (suspected) malignancies (70.9%). However, this spectrum of patients is representative for patients undergoing intravenous CECT in daily clinical practice in many institutions.[19,32] Secondly, in this study, the standard follow-up within seven days was not accurately performed in 68.9% (40/58) of the patients at risk. Because we collected the data for this study by following daily clinical practice, we were not able to interfere with clinical practice in order to perform accurate follow-up of kidney function in all patients. As we were not able to complete serum creatinine follow-up for all patients, it is possible that we underestimated CIN incidence. However, we were able to complete follow-up for the need of renal replacement therapy and outcome of death for all patients at risk for CIN.

Furthermore, we did not include controls who did not undergo intravenous CECT to evaluate causality between intravenous CECT, CIN incidence and mid-term effects. However, since CIN incidence was low (0.2%) and mid-term effects did not occur, we think that we have substantial evidence that CIN incidence and incidence of mid-term effects are not as relevant as has been assumed up till recently and there is no causality between intravenous CECT and nephropathy, renal replacement therapy and death. The addition of controls would not change this conclusion.

We did not perform a power analysis and considering the incidence of need for renal replacement therapy and death our sample size is relatively small.

## CONCLUSIONS

The number of patients at risk for CIN and CIN incidence was low. In addition, there were no mid-term effects following intravenous CECT. Our results imply that only a small group of patients would benefit from CIN prevention guidelines. In addition, mid-term effects following intravenous CECT are absent, making extensive CIN prevention guidelines seem superfluous. We therefore propose that only patients with severe chronic kidney disease stage 4-5 (eGFR < 30 ml/min/1.73 m²) should be considered to be at risk for CIN. We think

that the screening strategies for patients at risk should be tailored and the present strategy in which all patients are considered to be at risk for CIN should be replaced. Whether these patients (eGFR < 30 ml/min/1.73 $m^2$) would benefit from prophylactic intravenous hydration is questionable.

Further evidence to support this proposal should be acquired in a randomised controlled trial comparing at-risk patients receiving CIN prophylaxis with at-risk patients not receiving CIN prophylaxis. Thereby, also taking into account cost, complications of CIN and intravenous prophylactic hydration and health-related quality of life aspects.

## DISCLOSURES

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PHOTO QUIZ

# Something fishy

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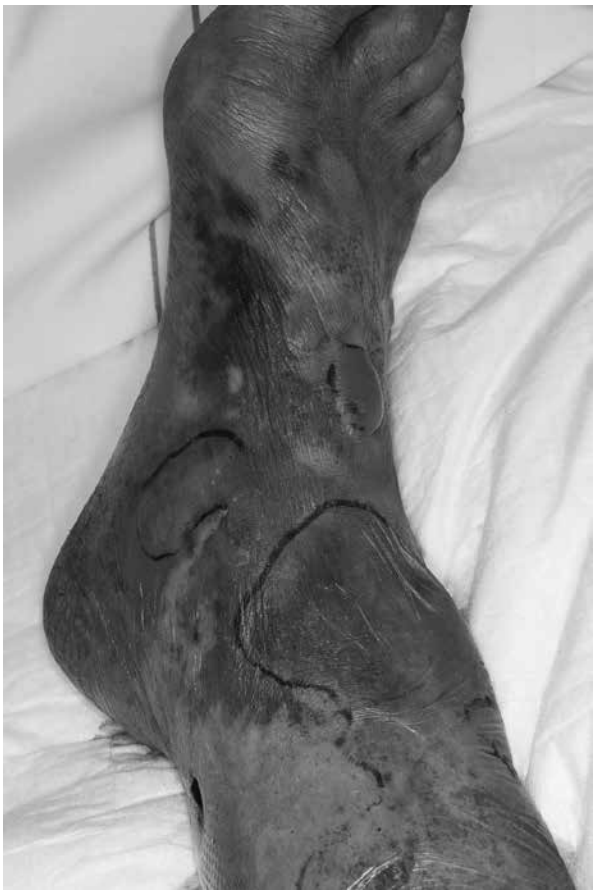
## CASE REPORT

A 57-year-old Caucasian male presented to our emergency department with hypothermia and circulatory failure. He had been well until the previous day; since then he felt lethargic and had noticed a painful discoloration on his right ankle. On examination purpura and blistering were identified (*figure 1*). Three days prior to admission, he visited the beach and walked barefoot along the shoreline; for dinner he had a ready-made tuna salad. The patient used alcohol excessively and smoked marihuana regularly. A putative diagnosis of severe septic shock due to cellulitis was made and he was admitted to the intensive care unit. Broad-spectrum antibiotics were prescribed, crystalloids were used for resuscitation and he was started on vasopressors. Surgical exploration was performed and necrotising fasciitis was excluded.

**Figure 1.** *Purpura and bullae over the lower extremities*



## WHAT IS YOUR DIAGNOSIS?

See page 376 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

# A small abscess with severe complications

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## CASE REPORT

A 24-year-old Somalian male, living in the Netherlands for two years, was admitted with a progressive headache and a suppurating abscess on the forehead, which had been present for six weeks.

The weeks before, this abcess had been incised twice and treatment with amoxicillin/clavulanic acid had been given (*figure 1*). However, the swelling increased in size and his condition deteriorated. He developed symptoms of nausea and vomiting, headache, drowsiness, impaired trunk balance and impaired motor function of the right arm and leg, without cough.

On physical examination he had a Glasgow Coma Scale score of E2M1V1, a temperature of 38 °C and neck stiffness. The swelling on the forehead was 3 inches in diameter, and he had a third nerve palsy. Further evaluation revealed a mildly elevated C-reactive protein (44 mg/l), a negative HIV test and normal chest X-ray.

A MRI scan of the cerebrum showed a large fluid collection in the subcutaneous tissue and the temporal muscle. A defect in the frontal bone communicated with an epidural fluid collection, causing a marked midline shift to the right. Along the left hemisphere there was meningeal thickening and enhancement (*figure 2*).

## WHAT IS YOUR DIAGNOSIS?

See page 377 for the answer to this photo quiz.

**Figure 1.** *Abscess on the forehead with small incision*

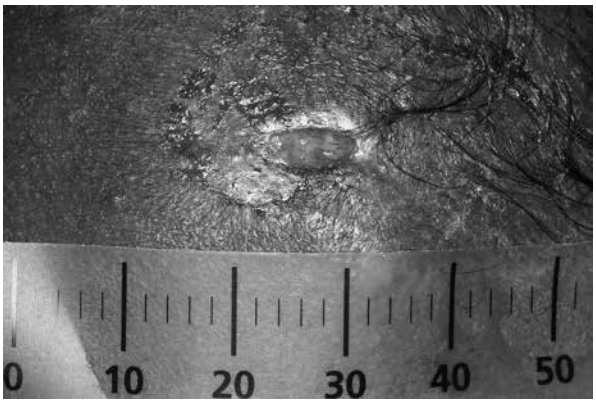


**Figure 2.** *MRI scan (transversal plane) of the cerebrum showing a fluid collection in the subcutaneous tissue and a midline shift to the right caused by an epidural fluid collection and meningeal thickening on the left side.*

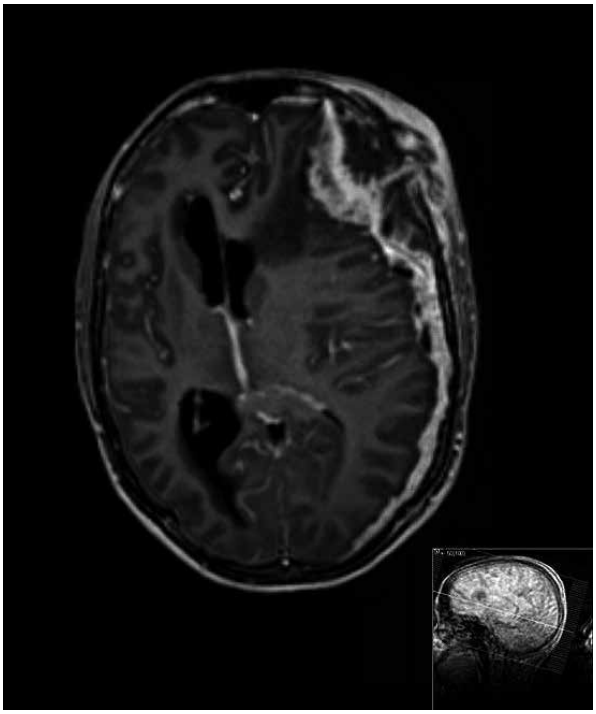

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PHOTO QUIZ

# An elderly lady with a scalp swelling

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## CASE REPORT

A 63-year-old female presented with a swelling on the left side of the scalp for the past two months. The swelling was gradually progressing in size and was painless. There was no history of headache, neurological deficits or B symptoms. On examination, there was a 3 x 3 cm bony hard swelling over the left parietal region of scalp. Her vital signs were stable and fundus examination was normal. Neurological examination did not reveal any signs of raised intracranial pressure, cranial nerve palsy or any focal neurological deficit. Her initial haematology and serum chemistry values were normal except for an elevated erythrocyte sedimentation rate of 135 mm/hour.

Magnetic resonance imaging of brain showed a well-defined, extra axial, soft tissue mass in the left parietal region, iso-intense on T1W (*figure 1*) and heterogeneously hyper-intense on T2W (*figure 2*).

## WHAT IS YOUR DIAGNOSIS?

See page 378 for the answer to this photo quiz.

**Figure 1.** *T1W MRI of the brain showing a well-defined, extra axial, iso-intense lesion adjacent to the right parietal cortex*

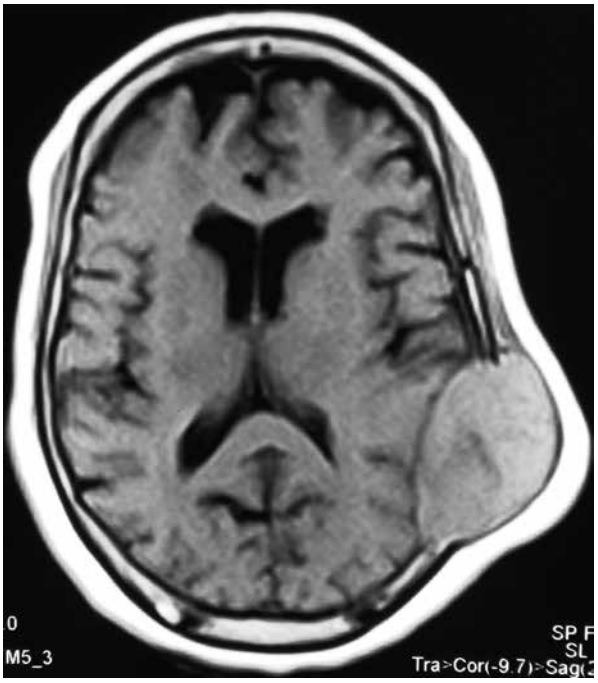


**Figure 2.** *The same lesion is heterogeneously hyper-intense on T2W MRI*

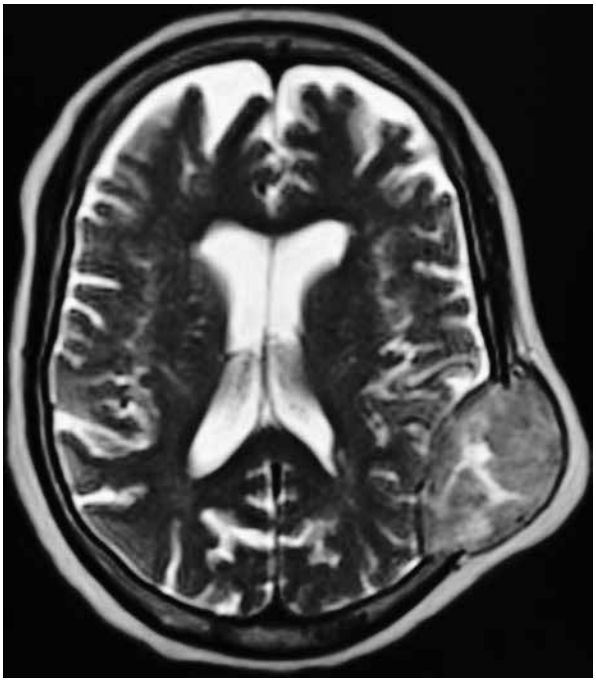

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PHOTO QUIZ

# Dysarthria, difficulty in walking and dizziness

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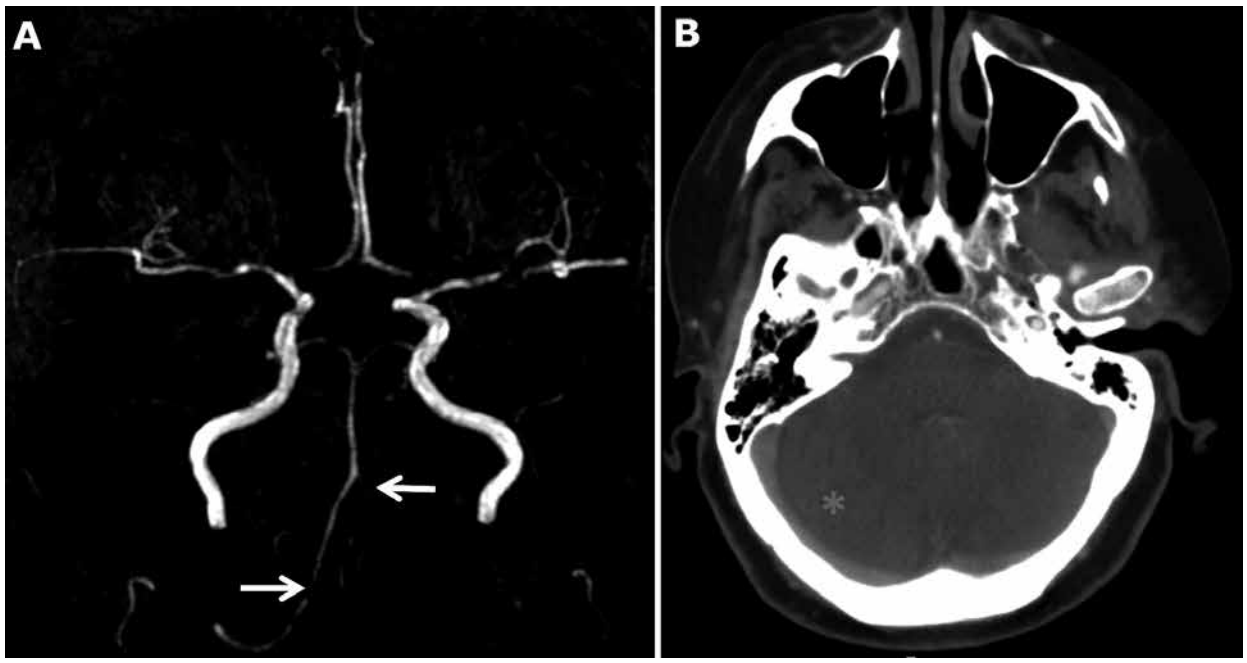
## CASE REPORT

A 75-year-old Dutch woman presented with dysarthria, difficulty in walking, vertigo, headache and vomiting. Until recently she was an active and relatively healthy woman. In a few weeks, she had become bedridden by her vertigo. She had been diagnosed with polymyalgia rheumatica by her general practitioner five months earlier for which she used a prednisolone weaning schedule (7.5 mg once daily at presentation). On physical examination a dysarthria, nystagmus, broad-based gait and word-finding difficulty were observed. Laboratory results showed an erythrocyte sedimentation rate (ESR) of 110 mm/h and C-reactive protein (CRP) level of 36 mg/l.

## WHAT IS YOUR DIAGNOSIS?

See page 379 for the answer to this photo quiz.

**Figure 1.** *Brain magnetic resonance angiography showing a bilateral occlusion of the vertebral arteries with retrograde filling of the right vertebral artery (A) with fresh ischaemia bilaterally in the cerebellum and occipital lobe (B, asterisk)*



ANSWER TO PHOTO QUIZ (PAGE 372)

SOMETHING FISHY

## DIAGNOSIS

Within 24 hours blood cultures and cultures of bullae contents grew *Vibrio spp*. Further testing resulted in the identification of *V. cholerae* and agglutination of the isolate showed that the serotype was neither O1 nor O139. On the 10th day of admission the patient died due to overwhelming sepsis with multi-organ failure and systemic candidiasis. Autopsy supported the clinical diagnosis along with cirrhosis of the liver.

*V. cholerae* is a comma-shaped, Gram negative, motile bacterium. Through agglutination, several morphologically and biochemically indistinguishable serotypes can be identified. Sources of *V. cholerae* are fresh, brackish or salt water and raw fish and crustaceans. *V. cholerae* O1 and O139 serotypes produce enterotoxins and cause mild to severe diarrhoea. In contrast *V. cholerae* non-O1, non-O139 (VCN) causes sporadic diarrhoeal illness but can result in septicaemia, wound infections, spontaneous bacterial peritonitis and cellulitis or necrotising fasciitis, usually in patients with cirrhosis or immunocompromised conditions.[1] Infection occurs due to ingestion of (raw/undercooked) seafood or water or direct contact with wounds or skin abrasions. The mortality rate is high (24-61%).[2,3] A possible mechanism underlying the observed virulence in cirrhotic patients is a higher bio-availability of iron which *Vibrio spp*. require for their reproduction.[1,4] We cultured the packaging of the ready-made tuna salad (recovered from the trash can), which was negative for *Vibrio spp*. *Vibrio spp* tend to be found in warmer water (> 17-20 °C) and VCN infections display a seasonal change with a peak in the warmer months.[1,5] The summer of 2013 was exceptionally warm with reported temperatures up to 36.9 °C; the temperature of the seawater on the day of his visit to the beach reached 22.1 °C. We speculate that he contracted the infection while visiting the beach, either wading through the water or by abrasion from a seashell. With reports indicating a rising sea surface temperature with changing microbiome in temperate regions it is possible that in the future this will be encountered more frequently.[6] Empirical coverage of *Vibrio spp* in a patient with a history of liver disease presenting with cellulitis and contact with (sea)water or raw seafood should be considered. For empirical treatment we recommend a third-generation cephalosporin, an *in vitro* synergistic effect with addition of a fluoroquinolone has been described.

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ANSWER TO PHOTO QUIZ (PAGE 373)

# A SMALL ABSCESS WITH SEVERE COMPLICATIONS

## DIAGNOSIS

The diagnosis of extrapulmonary tuberculosis was confirmed by a positive polymerase chain reaction and culture of the drained fluid for *Mycobacterium tuberculosis*. Our patient had an extensive tuberculosis with meningeal, epidural and bone localisation (*figures 3 and 4*). We started antituberculosis medication with rifampicin, pyrazinamide, ethambutol and isoniazid and in addition intravenous dexamethasone (20 mg once daily). After several days the diminished level of consciousness improved and his neurological symptoms recovered. After five weeks of therapy nearly all his symptoms had disappeared. The positive culture for *M. tuberculosis* was sensitive to all prescribed drugs.

In the Netherlands, migrants from Somalia have by far the highest annual incidence of tuberculosis (711 per 100,000) compared with all other population groups. They accounted for 18% of all diagnosed tuberculosis patients in 2012. Central nervous system tuberculosis is the most severe form of extrapulmonary tuberculosis; it accounts for about 1.5% of the annual cases of tuberculosis in the Netherlands (Mrs. E. Slump, Tuberculosis Surveillance Consultant, Royal Netherlands Tuberculosis Foundation, 2014; Personal communication by email). It is associated with a high mortality and severe neurological sequelae, particularly in multi-drug resistant (MDR) tuberculosis. In Somalia a high prevalence of MDR tuberculosis has been reported: 5.2% of the newly diagnosed pulmonary tuberculosis patients. However, in the Netherlands the proportion of MDR tuberculosis between 2000 and 2014 in Somalian migrants was only 1.7%, with two out of 147 patients in 2013. Rapid diagnosis and early treatment are crucial. Therefore, treatment should not be delayed and needs to be immediately started after direct auramine/Ziehl-Neelsen stain and the determination of polymerase chain reaction for *M. tuberculosis*, awaiting the results of tuberculosis culture and susceptibility testing, which usually takes several weeks.[1-3]

In our case, we had a doctors delay of three weeks, because an incision was made and antibiotics were given without performing the appropriate diagnostic tests. This case report shows how important it is to consider tuberculosis in skin abscesses in people originating from tuberculosis endemic countries. Even a small skin lesion can have major consequences, as shown in our patient.

**Figure 3.** *MRI scan (sagittal plane) of the cerebrum showing the epidural fluid collection and meningeal thickening*

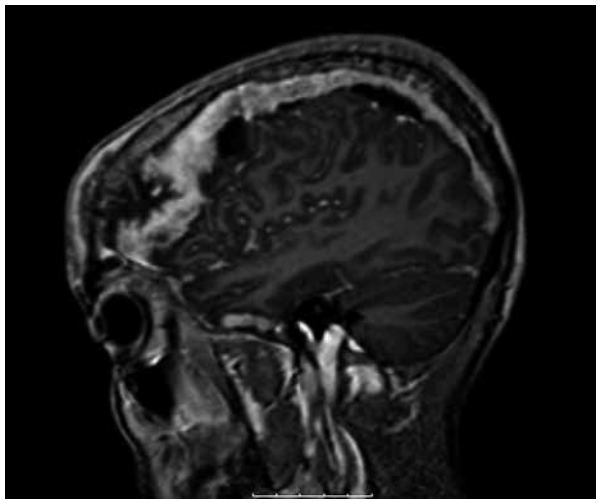
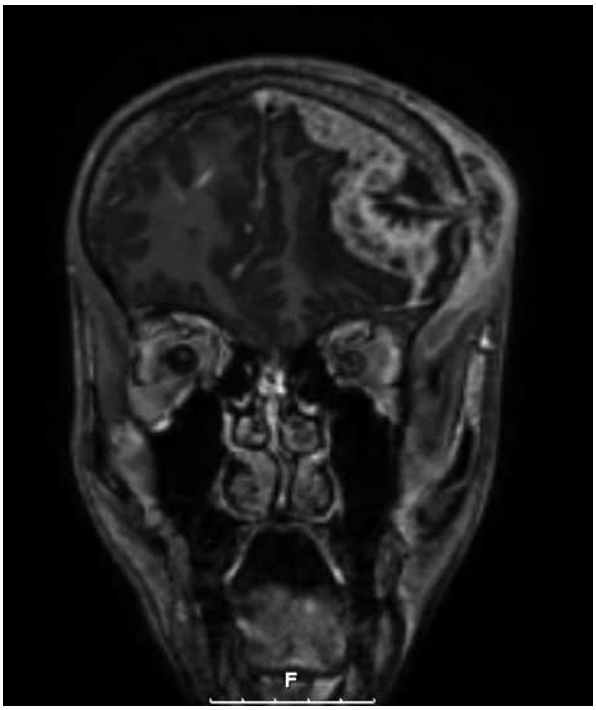


**Figure 4.** *MRI scan (coronal plane) of the cerebrum showing the midline shift to the right caused by the epidural fluid collection*

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ANSWER TO PHOTO QUIZ (PAGE 374)

# AN ELDERLY LADY WITH A SCALP SWELLING

## DIAGNOSIS

A biopsy from the lesion was performed, which showed sheets of plasmacytoid cells (*figure 3*), strongly expressing CD138 and Lambda light chain restriction (*figures 4 and 5*) and was negative for CD56 and cytokeratin, consistent with the diagnosis of Plasmacytoma. No other bony lytic lesions were detected on skeletal survey. However, serum protein electrophoresis showed monoclonal gammopathy with a serum M protein concentration of 3.54 g/dl. Her immunoglobulin assay was abnormal with an IgG fraction of 5455 mg/dl, IgA < 40 mg/dl, IgM < 25 mg/dl, free kappa measuring 11.5 mg/dl and an elevated free lambda light chain value of 75.1 mg/dl. Serum albumin was 3.7 g/dl, beta 2 microglobulin was 4.5 mg/ml and her bone marrow aspirate showed 42% plasma cells, all findings consistent with multiple myeloma ISS stage II.[1]

**Figure 3.** *Photomicrograph showing sheets of plasmacytoid cells (H&E x 200)*

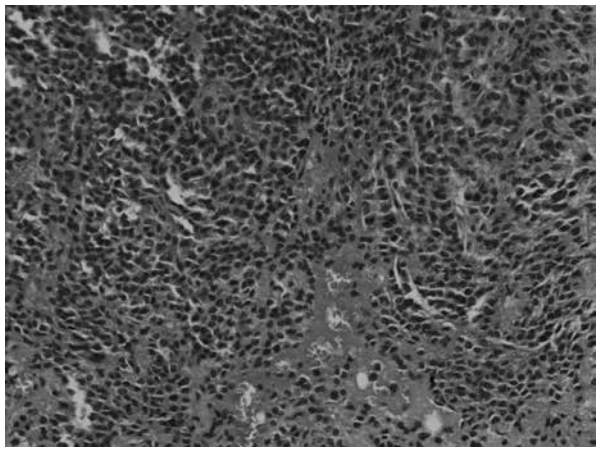


**Figure 4.** *Tumour cells show positivity for CD138 (IHC x 400)*

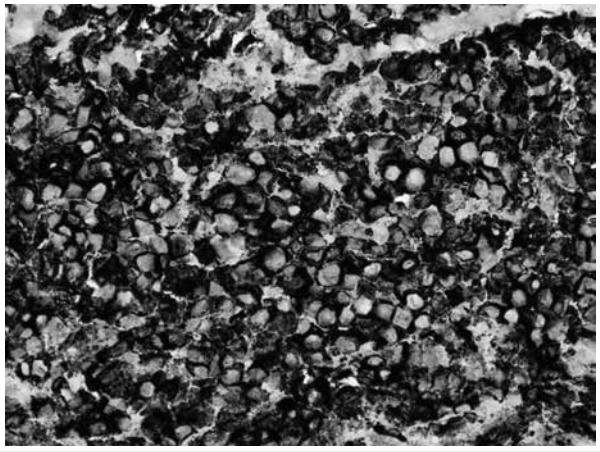
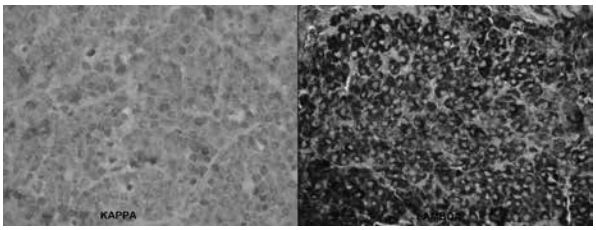


**Figure 5.** *Tumour cells showing Lambda light chain restriction (IHC x 400)*




Cranial plasmacytomas are rare lesions that can arise from the calvarium, dura or skull base and could be the harbinger of a more widespread systemic myeloma. Very rarely, it has been described as the sole presenting feature of underlying multiple myeloma. On imaging, these lesions can be confused with meningioma, cranial secondaries or lymphoma. Zigouris *et al*. described a case of an elderly male with cranial plasmacytoma, who presented with progressive right hemiparesis.[2] Similarly, Terada reported his experience with a patient who presented with gait disturbance. His cranial imaging revealed a plasmacytoma of the clivus of the skull compressing on the brain parenchyma.[3] There have been case reports where cranial plasmacytoma presented as isolated sixth nerve palsy.[4] Our patient also presented with the sole manifestation of an otherwise innocuous scalp swelling, which on systematic evaluation unearthed advanced multiple myeloma.

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ANSWER TO PHOTO QUIZ (PAGE 375)

DYSARTHRIA, DIFFICULTY IN WALKING AND DIZZINESS

## DIAGNOSIS

Magnetic resonance angiography revealed a bilateral occlusion of the vertebral arteries (*figure 1A*) with retrograde filling of the right vertebral artery, collateral formation and a divergent circle of Willis with fresh ischaemia bilaterally in the cerebellum and occipital lobe (*figure 1B*). A temporal artery biopsy confirmed giant cell arteritis (GCA). A diagnosis of bilateral cerebellar and occipital ischaemia as the consequence of bilateral vertebral arterial occlusion (BVAO) resulting from GCA was made. Treatment with high-dose pulse methylprednisolone was started after which the symptoms completely disappeared and the ESR and CRP level normalised.

BVAO is a rare complication of GCA and has a high mortality (75-80%).[1] 3% of GCA patients develop a (considered GCA related) cerebrovascular accident, of which 40-60% involves the vertebrobasilar area. Conversely, among 118 reported cases of non-traumatic BVAO, five cases (4.2%) were attributed to GCA.[1] The intracranial vertebrobasilar arteries are almost always spared from GCA (except the proximal 5 mm after the passage through the dura mater), possibly due to the significant rarefaction of the inner elastic layer.[1] The recognition of GCA as the underlying cause of BVAO may be difficult in part due to the relatively high prevalence of atherosclerosis in this older population. In our case, the patient had recently been diagnosed with polymyalgia rheumatica. Previous cases have been reported in which BVAO with associated neurological signs and symptoms were the first clinical manifestations of GCA.[1 (patient 1),2] Clinically, BVAO resulting from GCA differs from BVAO of arteriosclerotic origin by the much higher mortality rate (75% vs 19%, respectively), the presence of headache (100% vs 22%), fever (50% vs 0%) and an elevated ESR and not by neurological signs.[1] The slower evolution over time observed in arteriosclerotic BVAO allows the formation of collaterals supplying the otherwise perfusion-deprived vertebrobasilar territory. In GCA, the much more accelerated progression impedes the timely formation of collaterals which may itself contribute to the remarkably higher mortality of BVAO.[3] The spectrum of clinical manifestations in BVAO is wide and reflects the territories supplied by these arteries and includes visual disturbances, cranial nerve palsies, affection of the pyramidal and sensory tracts, cerebellar signs and altered consciousness. Due to the rareness of BVAO caused by GCA, therapy remains empiric and consists of prompt administration of high-dose corticosteroids. Additionally, anticoagulation and other immunosuppressive (as cyclophosphamide) therapy should be considered per individual patient in this highly fatal disease.

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CASE REPORT

# Hepatocellular carcinoma after danazol treatment for hereditary angio-oedema

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## ABSTRACT

Hereditary angio-oedema is characterised by recurrent episodes of laryngeal, intra-abdominal, facial or peripheral oedema. Danazol can be used as prophylaxis for recurrent attacks. Hepatotoxicity is a recognised adverse effect of danazol. We report an exceptional case of a danazol-induced hepatocellular carcinoma in a 75-year-old patient with hereditary angio-oedema.

## KEYWORDS

Hepatocellular carcinoma, HCC, danazol, hereditary angio-oedema, androgen therapy

**What was known on this topic?**
In the literature, only two cases of a danazol-induced hepatocellular carcinoma (HCC) in patients with hereditary angio-oedema have been described. HCC as a result of danazol has also been reported in patients with idiopathic thrombocytopenic purpura and systemic lupus erythematosus. We know that patients with an increased risk of HCC (such as patients with chronic hepatitis B and cirrhosis), should have an ultrasound of the liver every six months according to the Dutch HCC guideline. Chronic danazol use is not mentioned as an increased risk factor for HCC.

**What does this add?**
HCC is a rare side effect of long-term danazol treatment in patients with hereditary angio-oedema. This case report illustrates the importance of ultrasound monitoring of the liver in patients on long-term danazol treatment. Our suggestion is to add chronic danazol use to the increased risk group in the Dutch guideline for HCC, which implies that these patients should have an ultrasound of the liver every six months.

## INTRODUCTION

Hereditary angio-oedema is a potentially life-threatening disease and is characterised by recurrent episodes of laryngeal, intra-abdominal, facial or peripheral oedema.[1] Hereditary angio-oedema is caused by a deficiency or dysfunction of the C1 inhibitor.[1] Danazol can be used as long-term prophylaxis to prevent recurrent attacks of hereditary angio-oedema.[1] Hepatotoxicity is a recognised adverse effect of danazol, which can result in hepatitis with hepatocellular necrosis, cholestasis, and the development of adenomas, focal nodular hyperplasia and rarely hepatocellular carcinoma (HCC).[1,2] We report a patient with hereditary angio-oedema on long-term prophylaxis with danazol, who developed HCC.

## CASE REPORT

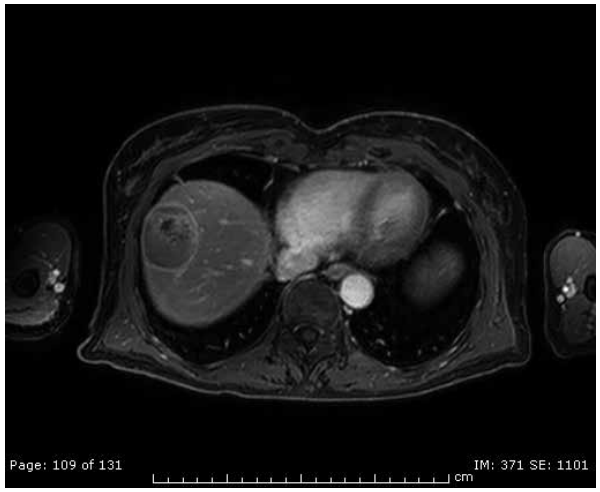
A 75-year-old woman, with a history of hereditary angio-oedema, was referred by her general practitioner to the emergency department because of pain in the right upper abdomen. The pain had existed for one day. She was on danazol 300 mg (accidental 400 mg) once daily for 33 years. She underwent annual liver ultrasound because of the (rare) risk of the development of a danazol-induced adenoma or HCC. The last ultrasound (nine months ago) showed gallbladder sludge, but no liver abnormalities.

On physical examination we saw a non-ill patient with tenderness in her right upper abdomen. Laboratory tests showed a slightly elevated aspartate aminotransferase and alanine aminotransferase. Ultrasound of the abdomen showed gallbladder sludge and a hyperechoic lesion with a hypoechoic rim of 4 x 4 cm in segment VIII of the liver. Additional blood tests (hepatitis A, B, C serology, alpha-fetoprotein) and an MRI of the liver were requested, because of the suspicion of HCC. Hepatitis serology was negative and alpha-fetoprotein was normal (2.90 μg/l; reference: < 20 μg/l). MRI showed a lesion of 4.1 x 4.6 x 4.2 cm in segment VIII of the liver with bulging of the liver capsule, without invasion in the vessels. The mass was slightly hyperintense on the T2-weighted sequences with centrally a few foci with varying intensity. After administration of contrast, we saw a heterogeneous enhancement in the arterial phase, with wash-out in the portal venous phase. In the late phase, there was capsular enhancement (*figure 1*), very suspect for HCC. There were no other suspicious lesions or signs of cirrhosis.

Resection of segment VIII and gallbladder (because of sludge) was performed. Danazol was stopped and patient was given an injection of Cynrize, a plasma-derived human C1 inhibitor, every three days to prevent perioperative angio-oedema. Pathological examination confirmed the diagnosis of HCC in a non-cirrhotic liver, which was radically removed.

The postoperative course was complicated by a subphrenic abscess, which was drained percutaneously. Hereafter, she recovered quickly. Remarkably, the patient had only minimal symptoms of angio-oedema in the four months after surgery, without medication.

**Figure 1.** *Axial T1-weighted magnetic resonance image (MRI) of the tumour in segment VIII of the liver with fat suppression in the late phase after intravenous contrast. There is a capricious staining and capsule visible around the central necrosis*




## DISCUSSION

HCC is a rare side effect of long-term danazol treatment in patients with hereditary angio-oedema. The much commoner causes of HCC, such as cirrhosis and viral hepatitis, should be excluded first. This case illustrates the importance of ultrasound monitoring of the liver in patients on long-term danazol treatment.

### Hereditary angio-oedema

Hereditary angio-oedema is an autosomal dominant disease, caused by mutations in the gene coding for C1 inhibitor located on chromosome 11. The incidence of hereditary angio-oedema is approximately 1:50,000.[3] There are two classical types of hereditary angio-oedema that result from deficiency (type I, 85%) or dysfunction (type II, 15%) of the C1 inhibitor, which results in excessive production of bradykinin (vasodilatory mediator).[1,3] The disease is characterised by recurrent episodes of angio-oedema, without urticaria or pruritus, which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts.[1,3]

### Danazol

Nearly all affected patients with hereditary angio-oedema are heterozygotes, which means that stimulation of the proper functioning gene can result in higher concentrations of C1 inhibitor. Such an effect can be achieved with the attenuated androgen danazol, the most frequently used long-term prophylactic agent in the treatment of hereditary angio-oedema.[1] Danazol is also used in the treatment of endometriosis, benign fibrocystic breast disease, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus.[1] Danazol was prescribed to 251 patients in the outpatient setting in the Netherlands in 2011.[4]

Described hepatotoxic side effects of danazol are hepatocellular necrosis, cholestasis, hepatocellular adenoma, focal nodular hyperplasia, and rarely HCC.[1,2] It is thought that androgens might have a direct mutagenic effect on the liver.[1] The magnitude of the risk of developing HCC from androgens cannot be determined, due to lack of data on this. The risk of developing hepatic adenomas in patients with hereditary angio-oedema on danazol is 7%, and the risk is about 26% if danazol is taken for more than ten years.[1] Malignant transformation is found in 4-16% of the adenomas;[5] however, there is also literature that suggests that malignant transformation of an adenoma is highly unlikely.[6]

In 1985, Buamah described a danazol-induced HCC for the first time, in a patient with endometriosis.[7] In the literature, two cases of a danazol-induced HCC in patients with hereditary angio-oedema have been described.[1,2] HCC as a result of danazol has also been reported in patients

with idiopathic thrombocytopenic purpura and systemic lupus erythematosis.[1]

**Hepatocellular carcinoma**

HCC is a primary tumour of the liver, which usually develops in the setting of chronic liver disease, particularly in patients with cirrhosis and/or viral hepatitis. In the absence of a surveillance program, HCC is frequently diagnosed late because of the absence of pathognomonic symptoms. Extrahepatic metastases are present at the time of the diagnosis in 5-15% of patients.[8,9] Resection of the HCC is the treatment of choice, but many patients are not eligible for resection because of extrahepatic metastases, anatomical constraints of the tumour, multifocal presence of the tumour, and/or poor underlying liver function.[10,11] Other curative treatment modalities are liver transplantation or radiofrequency ablation.[10,11] After curative treatment of HCC in a non-cirrhotic liver, as in this case, the three-year survival rate is 59%.[11] The presence of underlying cirrhosis is not associated with the survival rate and disease-free survival following potential curative treatment.[11] Recent work by Witjes *et al.* showed that immunohistochemical expression of several markers in HCC in a non-cirrhotic and cirrhotic liver was comparable.[12]

**Follow-up**

The international consensus meeting on hereditary angio-oedema[3] recommends annual liver ultrasound in patients on a daily danazol dose of 200 mg or less, and every six months in patients on doses higher than 200 mg. The patient in our case underwent annual liver ultrasound, whereas according to the consensus meeting biannual ultrasound was indicated. Patients with an increased risk of HCC, such as those with chronic hepatitis B and cirrhosis, should have an ultrasound of the liver every six months according to the Dutch guideline on HCC.[13] Chronic danazol use is not mentioned as an increased risk factor for HCC. Our suggestion is to add chronic danazol use to the increased risk group. In general, early detection of HCC is useful, because smaller tumours can be treated locally, and this increases the chance of survival.[13]

In conclusion, strict follow-up of patients on long-term danazol is recommended because of the risk of developing HCC. Diagnosis of danazol-induced HCC should be made after other causes such as cirrhosis and viral hepatitis have been excluded.

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## DISCLOSURES

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LETTER TO THE EDITOR

# Comment on treatment methods for ethylene glycol intoxication

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To the Editor,

We were very interested in the article by Rietjens *et al.*[1] regarding antidotal therapies utilised in the treatment of ethylene glycol and methanol intoxication. We were especially interested in the cost analysis of ethanol versus fomepizole treatment. In the United States (US), the use of ethanol is rare; either fomepizole or haemodialysis is utilised, with cost often the determining factor in deciding which to use.[2] At our facility we utilise a cost minimisation method for determining when to use haemodialysis versus fomepizole in minimally symptomatic patients. As an example, assume a theoretical patient: an 18-year-old male, 173 cm, weighing 70 kg. A 14.2 hour half-life for ethylene glycol following administration of fomepizole is assumed[3] and this formula, developed by Hirsch, *et al.*[4] to determine required dialysis time for removal of ethylene glycol to a serum level of 6 mmol/l (37.2 mg/dl) is used:

$T = [-V \ln (5/A)/0.06k]$

V = Watson estimate of total-body water in litres (41.25 l)

A = Initial toxin concentration in mmol/l (40.0 mmol/l)

k = 80% dialyser urea clearance in millilitres/minute at the initial observed blood flow rate (152 ml)

We compare medication, procedure, room, laboratory charges and risk of complications based on US national statistics. We assume a cost difference of 5% or less to be equivalent.

We calculated the time required for a serum ethylene glycol level of 180 mg/dl to fall to ≤ 20 mg/dl[5] to be ~44.6 hours. This would require a total of four doses of fomepizole.[6] At our hospital, the fomepizole regimen is administered on a general medical floor without telemetry.

Our haemodialysis patient would likewise receive an initial ethylene glycol level and the first dose of fomepizole while awaiting lab results. Per Hirsch,[4] an initial ethylene glycol level of 180 mg/dl could be dialysed to safe levels with a single 8-hour treatment. The patient would receive two additional fomepizole doses during his haemodialysis therapy.[7] At our hospital, a patient receiving dialysis would be placed in the intensive care unit.

Thus, the cost per dialysed patient is $ 15,053.79. With fomepizole only: the cost/patient is $ 15,657.00. The difference falls within our equivalency range of 5%.

**Table 1.** *Direct cost comparison by category for serum ethylene glycol 180 mg/dl*

| Cost category (US Dollars) | Fomepizole only | Haemodialysis and fomepizole |
|---|---|---|
| Room cost | 5998.00 (2x gen-med) | 3727.50 (1x ICU) |
| Medication | 9503.64 (x4 1.5 ml vials) | 7127.73 (x3 1.5 ml vials) |
| Labs | 156.00 (x3) | 104.00 (x2) |
| Procedure | | 2801.00 |
| Total | 15,657.64 | 13,760.73 |

**Sznajder et al.[8] note a complication rate during catheterisations of 8.1/100 patients and Klevins *et al.*[6] report an infection rate of 0.53/100/day. In 2005, inpatient facility and physician costs for haemodialysis catheterisation complications alone reached $ 12,957.[9] This adjusts from 2005 to 2013 (the year of our other charge data) to $ 14,983.28.[10]**

With an equivalent cost and greater safety associated with the pharmaceutical approach, we recommend fomepizole monotherapy in minimally symptomatic patients with an initial ethylene glycol level < 180 mg/dl. Costs and treatment protocols vary; therefore our level should not be considered a universal guideline for the addition of haemodialysis therapy. Rather, the methods employed in this analysis should be adapted by hospitals to implement cost-effective integration of haemodialysis into the treatment of patients with ethylene glycol poisoning.

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