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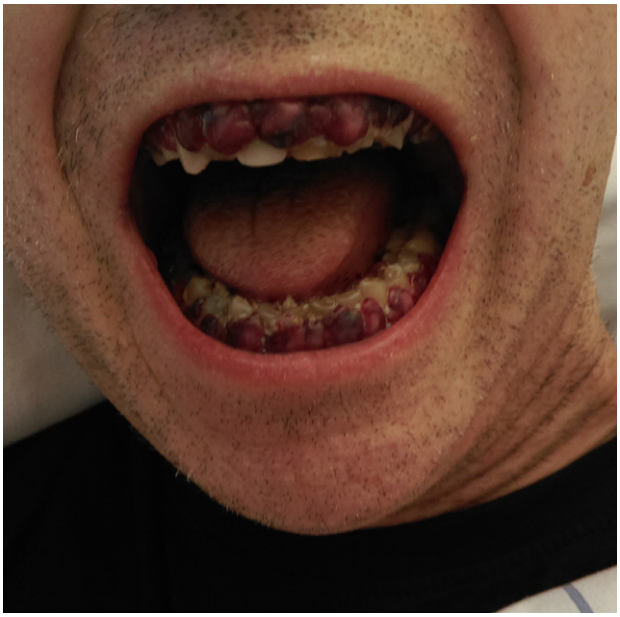

A referral from the dentist; what is your diagnosis?

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EDITORIAL

The need for collaborative research in transplantation medicine: illustrated by the immunosuppression conversion trials

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In this issue of the Netherlands Journal of Medicine, Bouamar et al.[1] report the results of their prematurely terminated randomised controlled trial in renal transplantation recipients on the early conversion of tacrolimus, a calcineurin inhibitor (CNI), to everolimus, a mammalian target of rapamycin inhibitor (mTORi), with concomitant withdrawal of steroids. An excess in acute rejections (30% versus 6.7%) resulted in the decision to terminate the study after the inclusion and randomisation of 60 of the intended 194 subjects.

Current standard immunosuppressive regimens in renal transplantation include CNIs and result in low rates of allograft rejection, and good long-term allograft survival. However, CNIs have chronic nephrotoxic effects and there is a search for further improvement of immunosuppressive regimens to reduce these adverse long-term effects. Late (i.e. more than one year after transplantation) conversion from CNI to mTORi showed no improvement in long-term renal function. Early conversion studied in the ZEUS trial showed better renal function with a benefit of 6.4 ml/min/1.73 m^2 for everolimus compared with cyclosporine five years after transplantation.[2] However, cyclosporine is no longer the most prescribed CNI in current transplantation care, as immunosuppression with low-dose tacrolimus, mycophenolic acid and prednisolone after daclizumab induction was found to result in superior renal allograft survival after 12 months compared with low-dose cyclosporine and low-dose sirolimus after induction or standard dose cyclosporine without induction.[3,4] The recently published ELEVATE trial is the largest study to date on early conversion from CNI to mTORi and included 715 subjects. No difference in renal function after one year was observed.[5] However, CNI and in particular tacrolimus treatment resulted in superior prevention of biopsy-proven acute rejection (BPAR) with a 2.4-fold increased risk in the everolimus arm. Long-term effects are awaited and are the main outcome of interest, especially with the tacrolimus subgroup as comparator, since tacrolimus is the standard CNI of choice. Tacrolimus was used as sole CNI in the study by Bouamar et al. and this could partially explain the high relative risk of rejection for everolimus.

Another important issue that needs to be mentioned is the concomitant withdrawal of steroids. The ELEVATE trial did not eliminate steroids which could be relevant for explaining the lower overall rate of biopsy-proven acute rejection. A recent Cochrane review discussed the effects of steroid withdrawal and concluded that there is no scientific basis to advise in favour of steroid withdrawal since it resulted in higher biopsy proven rejection rates and did not reduce the number of adverse effects. However, the overall quality of included studies was poor.[6] The study by Bouamar et al. resulted in an unacceptable acute rejection rate in the intervention arm within the first year after renal transplantation. This was obviously not the trial's intention, but a design based on the prevailing institutional protocol including steroid withdrawal unintentionally illustrated the lower limit of acceptable immunosuppression in an everolimus-based regimen. This negative trial is therefore relevant and should be published, even if one can question the initial design in hindsight.

THE NEXT STEP

Alternative strategies are being explored in order to reduce CNI exposure. The combination of lower tacrolimus dosing plus mTORi in combination with steroids seems promising. In the Cochrane review on CNI avoidance this strategy seems non-inferior in acute rejection risk and is associated with a lower incidence of viral infections.[7] The recently presented TRANSFORM study (2037 subjects) supports these data with similar allograft function and BPAR rates at one year after transplantation.[8] A more

definitive answer regarding the long-term effects on renal function is awaited. It should be noted that both tacrolimus and cyclosporine are used as CNI in the TRANSFORM study.[9]

In this editorial, we would like to highlight two observations that can be made with respect to the discussion above. First, few large collaborative efforts with harmonised protocols studying alternative strategies in immunosuppression after renal transplantation to optimise efficiency, validity and quality were initiated to address this topic. Looking back at the history of the CNI-mTORi conversion trials and steroid withdrawal studies, it is striking that there are multiple small studies with different designs, missing information and absent long-term follow-up data. A publication bias is likely to exist with negative results that never reached publication. Also, the inclusion of cyclosporine as CNI of choice does not aid in deciding whether the studied strategy is superior to tacrolimus-based regimens. Sub-analysis could address this issue, but only if studies are sufficiently powered.

Second, in the study of Bouamar et al. there were individuals that fared well by the studied regimen. What characterised them? Can they be identified shortly after transplantation to benefit from this regimen? The term *transplantomics* was coined several years ago; this suggests an aim of collective characterisation and quantification of the biology that translates into the function and dynamics of the graft and its recipient. In the mentioned trials deep phenotyping and genotyping of recipients and donors is lacking. Larger trials should include thorough (immuno)phenotyping and genotyping in order to come to individualised immunosuppression.

To maximise yield and optimise outcome for future renal transplant recipients, collaborations with molecular biology as well as between clinical institutions should be intensified.

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SPECIAL REPORT

Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT)

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ABSTRACT

The Dutch Working Party on Antibiotic Policy in collaboration with the Dutch Association of Chest Physicians, the Dutch Society for Intensive Care and the Dutch College of General Practitioners have updated their evidence-based guidelines on the diagnosis and treatment of community-acquired pneumonia (CAP) in adults who present to the hospital. This 2016 update focuses on new data on the aetiological and radiological diagnosis of CAP, severity classification methods, initial antibiotic treatment in patients with severe CAP and the role of adjunctive corticosteroids. Other parts overlap with the 2011 guideline. Apart from the Q fever outbreak in the Netherlands (2007-2010) no other shifts in the most common causative agents of CAP or in their resistance patterns were observed in the last five years. Low-dose CT scanning may ultimately replace the conventional chest X-ray; however, at present, there is insufficient evidence to advocate the use of CT scanning as the new standard in patients evaluated for CAP. A pneumococcal urine antigen test is now recommended for all patients presenting with severe CAP; a positive test result can help streamline therapy once clinical stability has been reached and no other pathogens have been detected. Coverage for atypical microorganisms is no longer recommended in empirical treatment of severe CAP in the non-intensive care setting. For these patients (with CURB-65 score >2 or Pneumonia Severity Index score of 5) empirical therapy with a 2nd/3rd generation cephalosporin is recommended, because of the relatively high incidence of Gram-negative bacteria, and to a lesser extent *S. aureus*. Corticosteroids are not recommended as adjunctive therapy for CAP.

KEYWORDS

Antimicrobial therapy, community-acquired pneumonia, guidelines

INTRODUCTION

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lower respiratory tract in patients outside a hospital or a long-term care facility, whereby a new infiltrate is demonstrated.[1,2] CAP is a common condition that carries a high burden of mortality and morbidity, particularly in the elderly.[2,3] In the Netherlands, approximately 250,000 patients develop pneumonia each year (https://www.volksgezondheidenzorg.info, 2 August 2017). This translates into an incidence of 15 per 1000 person-years. Worldwide, CAP remains the second cause of death and life years lost.[3]

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep Antibiotica Beleid), established by the Dutch Society for Infectious Diseases (VIZ), the Dutch Society for Medical Microbiology (NVMM) and the Dutch Society for Hospital Pharmacists (NVZA), coordinates activities in the Netherlands aimed at optimising antibiotic use, and containment of the development of antimicrobial resistance. In 2011 the SWAB and the Dutch Association of Chest Physicians (NVALT) published a joint guideline on the management of CAP. The present guideline is an update of this guideline, prepared by SWAB in collaboration with NVALT, the Dutch Society of Intensive Care (NVIC), and the Dutch College of General Practitioners (NHG).[1] See *textbox 1* for the methods.

Textbox 1

Methods and systemic literature review

The methods were identical to those of the previous version of these guidelines.[1] In short, these guidelines were drawn up according to the EBRO (Evidence Based Richtlijn-Ontwikkeling) and AGREE (Appraisal of Guidelines Research and Evaluation) recommendations for the development of guidelines.[43] A review of the existing national and international guidelines[24,25] was performed in addition to a literature search in PubMed database, Cochrane Register of Controlled Trials (CENTRAL), EMBASE, BMJ's Best Practice® and in Sumsearch® engine. For resistance surveillance data we utilised NethMap 2016.[10] Preparation of the guidelines text was carried out by a multidisciplinary committee consisting of experts delegated from the above-mentioned professional societies. After consultation with the members of the relevant professional societies, the definitive guidelines were drawn up by the delegates and approved by the boards of SWAB and NVALT. The full guidelines text, literature review and rebuttal of the received commentaries are available at www.swab.nl.

Revision was considered necessary because in the past few years new – for a significant part Dutch – data have been published on the differences between the various disease severity classification systems on the percentage of patients treated as severe CAP, the sensitivity of chest computed tomography (CT scan) for diagnosis, the role of atypical coverage in patients with severe CAP, and the role of adjunctive prednisone therapy. Therefore, the Guideline committee decided to update the recommendations on imaging, empirical treatment, and the use of corticosteroids in CAP. It should be stressed that other parts of the guideline were not updated and show a large overlap with the previously published 2011 guideline.[1] This is indicated for the relevant sections. See *textbox 2* for a short summary of all the new recommendations compared with the 2011 guideline.

The CAP guideline focusses on the initial treatment of suspected CAP in adult patients who present to the hospital, and are treated as outpatients, and hospitalised patients up to 72 hours after admission. Pneumonia in immunocompromised patients is outside the scope of this guideline.

CAUSATIVE BACTERIAL SPECIES OF CAP IN THE NETHERLANDS AND THEIR ANTIBIOTIC SUSCEPTIBILITY

Streptococcus pneumoniae remains the most commonly isolated bacterial pathogen causing CAP and should therefore always be covered in empirical treatment.[1] The annual number of registered Legionella infections in the Netherlands is stable at around 300 cases per year (http://www.rivm.nl/Onderwerpen/L/Legionella). From 2007 to 2010 the Netherlands experienced a large Q fever outbreak, caused by *Coxiella burnetii*, leading to a large number of hospital admissions, mostly for CAP, in those years. No other major shifts in the aetiology of CAP were observed in the last five years, although it should be emphasised that in up to half of CAP episodes no causative microorganism can be identified (*table 1*).[4-7] In patients with severe CAP and in patients who are admitted to the intensive care unit (ICU), *Legionella* spp., *Staphylococcus aureus* and Gram-negative infections are encountered more frequently compared with patients with mild to moderately severe CAP (*table 1*).[4-7] Recent retrospective data points to the need for increased awareness of *Aspergillus* infection as a complication of H1N1 influenza A virus infection in critically ill patients on the ICU.[8] It should be noted that the occurrence of atypical pathogens (*Legionella* spp., *C. burnetii, Mycoplasma pneumoniae,* and *Chlamydia/Chlamydophila* species) in patients admitted to the ward with a CURB-65 score of ≥ 3 is very low (*table 1*).[9]

The resistance percentage of *S. pneumoniae* for erythromycin is 12%, for co-trimoxazole 7% and for

Textbox 2

- What's new since the 2011 guidelines were published? *S. pneumoniae* remains the most common isolated bacterial cause of CAP in the Netherlands. In patients with severe CAP or patients who must be admitted to the ICU, *Legionella* spp. (up to 6%), *S. aureus* (up to 10%) and Gram-negative infections (up to 20%) are encountered more frequently than in patients with mild or moderate severe CAP. No aetiological agent can be identified in up to half of the episodes of CAP. The large Q fever outbreak in the Netherlands, which started in 2007, came to an end in 2010. No major shifts in resistance patterns of the most common causative agents of CAP were observed in the past 5 years in the Netherlands.
- Patients with CAP may be classified according to severity: I) mild, II) moderately severe, III) severe CAP admitted to the ward and IV) severe CAP admitted to the intensive care unit (ICU). Two validated scoring systems are in use: the Pneumonia Severity Index and the CURB-65. Alternatively, a pragmatic classification (treatment at home; admission to a general medical ward and admission to ICU) can be used. The committee does not recommend any of these scoring systems over the others; however, we recommend that each hospital uses only one scoring system consistently in daily practice.
- For patients with risk category III (severe CAP – ward admission; CURB-65: 3-5; PSI: 5; hospitalised on non-ICU ward) therapy should be started with a 2nd or 3rd generation cephalosporin. No empirical coverage for atypical microorganisms is given. A Legionella and pneumococcal urinary antigen test should be carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella* spp. is recommended. If the pneumococcal urinary antigen test is positive, therapy can be narrowed to penicillin or amoxicillin. If both are negative, therapy is continued with a 2nd or 3rd generation cephalosporin, to provide additional coverage for *Enterobacteriaceae* and to a lesser extent *S. aureus*.
- For patients with category IV (severe CAP – ICU admission; hospitalised on ICU ward) it is always recommended to cover *S. pneumoniae, Legionella* spp. and Gram-negative infections. For this purpose there are two equally acceptable choices, both with excellent antimicrobial activity against all expected causative agents: (a) monotherapy with moxifloxacin or (b) combination therapy with a 2nd or 3rd generation cephalosporin and ciprofloxacin. Macrolides are no longer recommended in this patient category. For all patients in category IV, a Legionella urinary antigen and *S. pneumoniae* urine antigen test is carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella* spp. is recommended. If the Legionella test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella* spp.) because the sensitivity of the urinary antigen test is not 100%. Since the specificity of the pneumococcal urine antigen test is < 100%, antibiotic treatment can be streamlined to penicillin or amoxicillin only in patients with a positive test result and without another pathogen detected once clinical stability (often within 48 hours) has been reached.
- Corticosteroids are not recommended as adjunctive therapy for treatment of CAP.

doxycycline 9%.[10] Resistance to levofloxacin and moxifloxacin is very uncommon. In the Netherlands, high-level penicillin-resistant *S. pneumoniae* is extremely rare (< 1%) and thus does not require coverage by empirical antibiotic therapy. High-level resistance to penicillin should be considered in patients not – or insufficiently – responding to empirical treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients, increasing the dosage of penicillin or a switch to a cephalosporin should be considered.

SEVERITY OF DISEASE UPON PRESENTATION IS USED FOR THE CHOICE OF INITIAL TREATMENT

Patients with CAP may be classified according to severity: mild, moderate-severe and severe CAP. Selection of empirical antibiotic therapy should be guided by the severity of the disease at presentation. Three scoring systems are in use. The Pneumonia Severity Index (PSI or Fine score) and the CURB-65 score (*table 2*)[1,11-13] are validated scoring systems, equally reliable in predicting

Table 1. *Most common aetiologies of community-acquired pneumonia in the Netherlands according to study population*

	Study population		
	Community	**Hospital**	**ICU**
	1 study[4]*	**2 studies[5,9]**	**1 study[7]**
S. pneumoniae	6%	8-24%	22%
H. influenzae	9%	3-5%	7%
Legionella spp.	0%	1-6%	1%
S. aureus	0%	1-2%	10%
M. catarrhalis	0%	0-1%	0%
Enterobacteriaceae	0%	2-5%	8%
Pseudomonas aeruginosa	0%	0-2%	5%
M. pneumoniae	9%	1-3%	0%
Chlamydophila spp.	2%	0-7%	0%
C. burnetii	0%	0-14%	1%
Viral (e.g. Influenza)	37%	3-5%	17%
Other	2%	2-3%	10%
No pathogen identified	33%	63-65%	25%

Data on the hospital and intensive care unit study populations were derived from studies published between 2011 and 2016, data on the community were derived from a study published in 2004. *This study included patients with a lower respiratory tract infection in general practice, no standard chest X-ray was performed for the diagnosis of CAP.

30-day mortality in patients hospitalised with CAP.[14-16] Alternatively, a pragmatic classification (treatment at home; admission to a general medical ward and admission to an ICU) can be used. It should be noted that there can be marked differences in the categorisation of severity using these different scoring systems. For instance, a Dutch study among 1047 patients admitted with CAP showed that using a CURB-65 score > 2 as cut-off, almost twice as many patients were classified as having severe CAP as compared with the PSI score.[17] However, with a cut-off CURB-65 score of > 3 less patients were classified as severe CAP compared with the PSI. As there is no gold standard, the committee does not recommend any of the scoring systems over the other; however, it is recommended that each hospital consistently uses only one of these scoring systems in daily practice. These recommendations are identical to the previous guideline.[1]

RADIOLOGICAL INVESTIGATIONS IN THE DIAGNOSTIC WORK-UP OF PATIENTS SUSPECTED FOR CAP

The chest X-ray does not allow prediction of the causative microorganism in CAP.[18,19] The wider availability of low-dose CT scan facilities at emergency departments will likely lead to increased use of CT scanning of the chest in patients presenting with respiratory symptoms, and may ultimately replace the conventional chest X-ray. Recent data show that an early CT scan can improve diagnostic accuracy compared with chest X-ray.[20] However, at present, there is not enough evidence to advocate the use of CT scanning as the new standard in patients evaluated for CAP. For patients with clinical features of CAP but without signs of infection on the initial chest X-ray, an additional chest X-ray within 48 hours may help to establish the diagnosis of CAP.[21]

MICROBIOLOGICAL INVESTIGATIONS

Although interpretation of Gram's stain of sputum may allow early identification of the bacteriological cause of CAP, it is not recommended for guiding initial treatment. However, before starting antimicrobial therapy, blood and, if possible, sputum specimens should be obtained for culture, because culture results enable streamlining of antibiotic therapy and a switch to oral therapy if a specific pathogen is isolated. PCR results from nasopharyngeal swabs are considered the most reliable indicator for influenza virus replication in the human body.[22,23] Validated PCR tests for respiratory viruses and atypical

Table 2. *Validated scoring systems to measure the severity of disease in patients with CAP: the CURB-65 and Pneumonia Severity Index*[1,11,12]

CURB-65	**CURB-65 criteria**		
	Confusion: defined as a new disorientation in person, place or time		
	Urea > 7 mmol/l		
	Respiratory rate ≥ 30 / min		
	Blood pressure: Systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg		
	Age ≥ 65		
	Core criteria	**Score CURB-65**	**30-day mortality**
	No core criteria	0	0.7%
	One core criterion	1	3.2%
	Two core criteria	2	3%
	Three core criteria	3	17%
	Four core criteria	4	41.5%
	Five core criteria	5	57%
Pneumonia Severity Index (PSI or Fine score)	**Step 1: Patient with community-acquired pneumonia**		
	If presence of <u>any</u> of the following proceed to step 2, if all are absent assign to risk class I: over 50 years of age; altered mental status; pulse ≥ 125/min; respiratory rate > 30/min; systolic blood pressure < 90 mmHg; temperature < 35°C or ≥ 40°C and/or a history of neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, liver disease		
	Step 2: Point scoring system (Characteristic and points assigned)		
	Age: Age in years (male); Age in years –10 (female)		
	Coexisting conditions: Neoplastic disease + 30; liver disease + 20; congestive heart failure + 10; cerebrovascular disease +10; renal disease + 10		
	Physical examination: Altered mental status + 20; respiratory rate ≥ 30 / min + 20; systolic blood pressure < 90 mmHg + 20; temperature < 35°C or ≥ 40°C + 15; pulse ≥ 125 / min + 10		
	Laboratory and radiological findings: arterial pH < 7.35 + 30; urea ≥ 11.0 mmol/l + 20; sodium < 130 mmol/l + 30; glucose ≥ 14.0 mmol/l + 10; haematocrit < 30% + 10; partial oxygen pressure < 60 mmHg + 10; pleural effusion + 10		
	Step 3. Calculation of 30-day mortality		
	Risk class	**Total score**	**Mortality**
	I	Not applicable	0.1%
	II	≤70	0.6%
	III	71-90	0.9%
	IV	91-130	9.3%
	V	>130	27.0%

pathogens are preferred over serological tests. A urinary antigen test for *Legionella* spp. should be performed in all patients with severe CAP.[24-27] One should, however, be aware that in the early stages of the disease the Legionella urinary antigen test may be falsely negative, especially in patients with mild pneumonia. In addition, with the current widely used test (immunochromatographic assay) only *L. pneumophila* type 1, which accounts for approximately 90% of Legionella cases, can be detected.

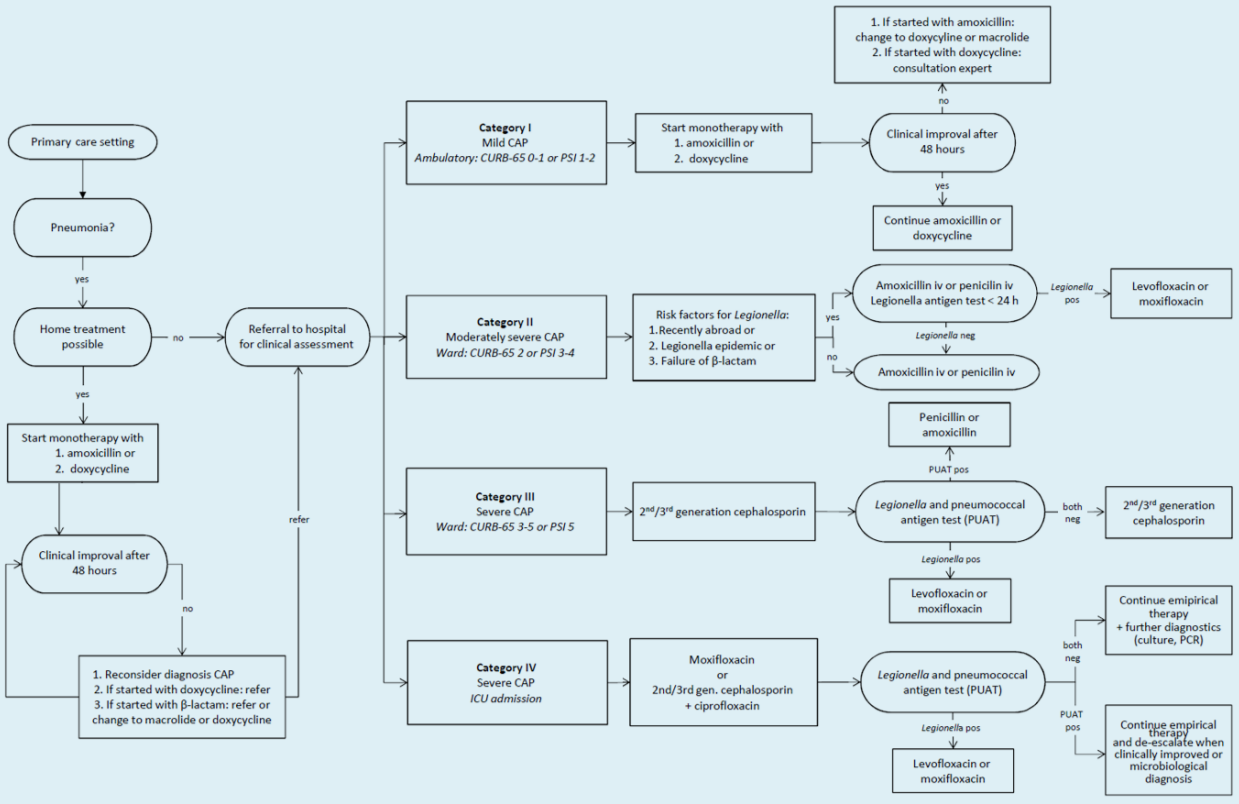
While the above recommendations have not changed compared with the previous guidelines,[1] the usefulness of the urinary pneumococcal antigen test has been reconsidered. The sensitivity of the urinary pneumococcal antigen test for demonstrating a causative role of *S. pneumonia* in adult patients is low, but the test is highly specific.[28-31] It has to be noted, however, that urinary pneumococcal antigens may be detectable in children, and also in adult patients with exacerbations of chronic obstructive pulmonary disease

without pneumonia.[32] It is now recommended to perform an urinary antigen test for *S. pneumoniae* in all patients treated for severe CAP. In patients with a positive test result and without another pathogen detected, antibiotic treatment can be simplified to amoxicillin or penicillin when the patient is treated on the ward. For patients on the ICU, therapy is de-escalated once clinical stability has been reached, which is often within 48 hours (*figure 1*).

EMPIRICAL ANTIBIOTIC THERAPY FOR CAP

As compared with the previous guidelines, the most important change in the recommended empirical antibiotic therapy for CAP is to start with 2nd or 3rd generation cephalosporin monotherapy instead of combination therapy with amoxicillin or penicillin together with a quinolone or erythromycin in patients with severe CAP who are treated in a non-ICU ward. From an antibiotic stewardship perspective this is an important gain. The main reason for this change is the very low incidence of atypical pathogens in patients admitted to the ward with CURB-65 score ≥ 3 as outlined above. This is supported by the recent findings from the Dutch CAP-START study, involving more than 2000 patients with clinically suspected CAP admitted to non-ICU wards; in this study empirical treatment with beta-lactam monotherapy was non-inferior to strategies with a beta-lactam-macrolide combination or 4th generation fluoroquinolone

Figure 1. *Flow chart of guideline recommendations on empirical antibiotic treatment of CAP*



- When no improvement is seen after two courses of antibiotics in the primary care setting, is it advised to consult an expert (internist-infectiologist, microbiologist or pulmonologist).
- Macrolides should not be used as initial therapy in mild CAP. They can be used in the event of penicillin allergy and when doxycycline cannot be used due to pregnancy or lactation. If doxycycline is given, start with a loading dose of 200 mg.
- In the event of penicillin allergy in moderately severe CAP, administer a 2nd or 3rd generation cephalosporin or moxifloxacin.
- High-level resistance to penicillin should be considered in patients not – or insufficiently – responding to empirical treatment with penicillin or amoxicillin and with a recent travel history abroad. In such patients increasing the dosage of penicillin (2 million IU 6 dd, or continuous infusion) or a switch to a cephalosporin (e.g. ceftriaxone 2 g once daily) should be considered.
- In the event of aspiration, the possibility of anaerobes or *Enterobacteriaceae* should be taken into account: penicillin or cephalosporins are replaced by amoxicillin-clavulanate.
- In the case of fulminant pneumonia after an episode of influenza, penicillin is replaced by a beta-lactam antibiotic with activity against *S. aureus*.
- In patients with moderately severe or severe CAP with documented colonisation of the respiratory tract with *Pseudomonas* spp., ceftazidime or ciprofloxacin should be added if not otherwise given.
- Antiviral treatment with oseltamivir is recommended for patients with confirmed or suspected influenza who have complicated illness with respiratory insufficiency (please refer to the guidelines from the National Institute for Public Health and Environment 'LCI richtlijn influenza', 2011).
- The recommended treatment options for severe CAP on the ICU are considered to be two equally acceptable choices.
- *Legionella* pneumonia should be treated with a fluoroquinolone. Most evidence is available for levofloxacin.
- De-escalate empirical antibiotic therapy when clinically improved or definitive microbiological diagnosis is made. Please also refer to SWAB Guidelines for Antimicrobial Stewardship, 2017.

Table 3. *Guidelines for the choice of initial therapy for community-acquired pneumonia*

Severity	Antibiotic	Route	Dose	Frequency
Category I: mild pneumonia				
1st choice	Amoxicillin	Oral	750 mg	q8h
2nd choice	Doxycycline	Oral	100 mg (first dose 200 mg)	q24h
Category II: moderately severe pneumonia				
	Penicillin	IV	1 MU	q6h
	Amoxicillin	IV	1000 mg	q6h
Category III: severe pneumonia (ward)				
Monotherapy	Cefuroxime *or* Ceftriaxone *or* Cefotaxime	IV IV IV	1500 mg 2000 mg 1000 mg	q8h q24h q6h
Category IV: severe pneumonia (ICU)				
Monotherapy	Moxifloxacin	IV / oral	400 mg	q24h
Combination therapy	Cefuroxime *or* Ceftriaxone *or* Cefotaxime *and* Ciprofloxacin	IV IV IV IV	1500 mg 2000 mg 1000 mg 400 mg	q8h q24h q6h q12h

monotherapy with regard to 90-day mortality.[9] However, these data also indicated that Gram-negative bacteria and *S. aureus* are a more frequent cause of CAP among patients on the ward admitted with severe CAP when compared with patients with moderately severe CAP (CAP-START study, unpublished data) and, therefore, these pathogens should be covered in empirical therapy. Especially in patients with severe CAP, Legionella infection can be reliably ruled out with the urinary antigen test. To summarise, the recommendations for the empirical antibiotic therapy of the following four categories of CAP are as follows (*table 3, figure 1*):

Risk category I (mild CAP): CURB-65: 0-1, PSI: 1-2, non-hospitalised

For this group, initial therapy with a narrow spectrum beta-lactam antibiotic (1st choice) or doxycycline (2nd choice) is recommended. This is in accordance with the previous guidelines[1] and the 2011 guidelines for patients treated by GPs.[33] Doxycycline is not a first choice for this group in view of the 9% resistance of *S. pneumoniae* against doxycycline. The choice of a drug active against the most frequently occurring causative agent (*S. pneumoniae*) is essential in this case. Oral penicillin is not considered a first choice in view of the suboptimal gastrointestinal resorption. As a result of the increasing resistance of pneumococci against macrolides (10-14%), monotherapy with macrolides is discouraged unless the patient is allergic to penicillin and it is not possible to administer doxycycline (e.g. because of pregnancy or lactation). In that case, either clarithromycin or azithromycin are preferred. If there is a strong clinical suspicion of *Legionella* infection, then the Legionella urine antigen test must be carried out and empirical therapy must be adjusted. For patients in risk category I who receive amoxicillin or penicillin as initial therapy but do not improve within 48 hours, therapy should be switched to monotherapy with a macrolide or doxycycline. If therapy was initiated with doxycycline a switch to macrolides is not rational. In that case, referral to a hospital must be considered.[1] In the outpatient setting, coverage for *S. aureus* in the influenza season, e.g. by amoxicillin-clavulanate, is not indicated.

Risk category II (moderate-severe CAP): CURB-65: 2, PSI: 3-4, admitted to non-ICU ward

For this category, initial therapy should be beta-lactam monotherapy, and the first choice is either intravenous penicillin or amoxicillin. Doxycycline and macrolides cannot be recommended because of the increasing pneumococcal resistance. Broad-spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime are not recommended because the expected

pathogens do not justify the broader spectrum. In case of penicillin allergy, the best alternatives are a 2nd or 3rd generation cephalosporin or a 4th generation quinolone. If a patient of category II has one or more of the following risk factors for *Legionella* spp. a Legionella antigen test should be performed within 24 hours: 1) a recent visit to a foreign country, 2) coming from an epidemic setting of *Legionella* spp. infections, 3) failure to improve despite ≥ 48 hours of treatment with a beta-lactam antibiotic at an adequate dosage without evidence of abnormal absorption or non-compliance. If the Legionella antigen test is positive, therapy must be switched to monotherapy directed against *Legionella* spp. For Legionella pneumonia, levofloxacin has the most clinical evidence to support its use.

Risk category III (severe CAP): CURB-65: 3-5, PSI: 5, admitted to non-ICU ward

Therapy should be started with a 2nd or 3rd generation cephalosporin, because of the higher incidence of Gram-negative bacteria, and to a lesser extent *S. aureus*, in this patient group. For all patients in category III, a Legionella and pneumococcal urinary antigen test should be carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella* spp. is recommended. If the pneumococcal urinary antigen test is positive, therapy can be narrowed to penicillin or amoxicillin. If both are negative, therapy should be continued with a 2nd or 3rd generation cephalosporin.

Risk category IV (severe CAP): admission to ICU

In this category, it is always recommended to cover *S. pneumoniae, Legionella* spp., *S. aureus* and Gram-negative bacteria. For this purpose there are two equally acceptable choices, both with excellent antimicrobial activity against all the expected causative agents. The choice is dependent, on the one hand, on the risk of development of antimicrobial resistance at the population level; on the other hand, the costs, the ease of administration and the profile of side effects play an important role:

- Monotherapy with moxifloxacin or
- Combination therapy with a 2nd or 3rd generation cephalosporin and ciprofloxacin.

Moxifloxacin is preferred over levofloxacin because of its high activity against pneumococci, favourable pharmacodynamic characteristics and good tissue penetration. Potential prolongation of the QT interval should be taken into account. Because of the high rate of side effects associated with their intravenous administration, macrolides are no longer recommended in this patient category.

For all patients in category IV, a Legionella urinary antigen and *S. pneumoniae* urine antigen test is carried out as a routine procedure within 12-24 hours of admission. If the Legionella test is positive, monotherapy directed against *Legionella* spp. is recommended. If the Legionella test is negative, the patient is still treated further with combination therapy (coverage of both *S. pneumoniae* and *Legionella* spp.) because the sensitivity of the urinary antigen test is not 100%. Since the specificity of the pneumococcal urine antigen test is < 100%, antibiotic treatment can be streamlined to penicillin or amoxicillin only in patients with a positive test result and without other pathogens detected if clinical stability (often within 48 hours) has been reached, or pneumococci have been cultured. In the event of a culture-proven causative agent, pathogen-directed antibiotic treatment is to be preferred at all times.

TIMING OF FIRST DOSE OF ANTIBIOTICS, TREATMENT DURATION AND SWITCH FROM INTRAVENOUS TO ORAL ROUTE

This section has not been altered compared with the 2011 guidelines.[1] All patients should receive antibiotics as soon as the diagnosis of CAP is established. For patients with severe CAP admitted through the emergency department (ED), the first antibiotic dose should be administered within four hours of presentation and preferably while still in the ED. In patients with sepsis and septic shock, the recommendation of the Surviving Sepsis Campaign guidelines applies.[34] Although the guidelines emphasise the importance of initiating antibiotic treatment rapidly, maximal efforts should be made to avoid inaccurate diagnosis of CAP and/or inappropriate utilisation of antibiotics.

If adult patients with mild to moderate-severe CAP are treated with a beta-lactam antibiotic or fluoroquinolones, the length of antibiotic treatment can be shortened to five days in those patients who have substantially improved after three days of treatment.[35-37] Pneumonia caused by *S. aureus* should be treated for at least 14 days.[25] Pneumonia caused by *M. pneumoniae* or *Chlamydophila* spp. is generally treated for 14 days,[25] but no studies on treatment duration have been performed for these agents. For Legionella pneumonia a treatment duration of 7-10 days is sufficient in patients with a good clinical response.

Patients should be switched from intravenous to oral therapy when they have substantially improved clinically, have adequate oral intake and gastrointestinal absorption

and are haemodynamically stable.[38,39] For patients who fulfil these criteria, inpatient observation after switching to oral therapy is not needed.[25,40]

THE ROLE OF ADJUNCTIVE CORTICOSTEROIDS FOR PATIENTS WITH CAP

Over the last decade a whole range of potential immunomodulating therapies as adjunctive to antibiotics have been investigated in patients with CAP. Most data are available on the potential efficacy of corticosteroids. The three largest studies on adjunctive therapy with corticosteroids in patients with CAP[5,41,42] yielded statistically significantly faster defervescence and, thereby, a shorter time to clinical stability and/or a shortening of length of hospital stay by one day for patients treated with corticosteroids. However, symptom resolution, overall cure rates, complication rates, ICU admission and mortality did not differ between patients with or without corticosteroid treatment. In all studies, the risk of hyperglycaemia was significantly higher in the corticosteroid-treated patients. In addition, treatment with short-term, high-dose corticosteroids may lead to other side effects, once applied routinely in larger populations. Therefore, the guidelines committee concluded, based on the available data, that the relatively small short-term benefits of adjunctive corticosteroids do not outweigh the potential disadvantages. As a result, the guidelines do not recommend corticosteroids as adjunctive therapy for treatment of CAP.

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DISCLOSURES

Members of the preparatory committee reported the following potential conflicts of interest:
MJB: Novartis Europe advisory board Daptomycin, Pfizer Netherlands advisory board vaccines, grant from Pfizer Netherlands for investigating aetiology of CAP; WGB: received a grant from GSK and Astra Zeneca for research and a fee from Pfizer for medical advice; EMWG: grant from GSK for investigating aetiology of CAP; TJV: received two grants for research and a fee for consultation from Pfizer; APES: received support for conference attendance from Pfizer and AstraZeneca.
The other authors have no competing interests.

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ORIGINAL ARTICLE

Conversion from tacrolimus to everolimus with complete and early glucocorticoid withdrawal after kidney transplantation: a randomised trial

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ABSTRACT

Background: While conversion from cyclosporine to everolimus is well documented, conversion from tacrolimus has been poorly studied. In this randomised, controlled trial the safety and tolerability of switching from tacrolimus to everolimus with glucocorticoid withdrawal after living-donor kidney transplantation was studied.

Methods: A total of 194 patients were planned to be randomised 1:1 to either continue tacrolimus or to convert to everolimus at month 3 after transplantation. At randomisation, all patients received tacrolimus, mycophenolate mofetil and prednisolone. Everolimus was started in a dose of 1.5 mg twice daily, aiming for predose concentrations of 4-7 ng/ml. Prednisolone was gradually withdrawn in both groups.

Results: The trial was stopped prematurely after the inclusion of 60 patients. The interim analysis showed an unacceptably high rejection rate in the everolimus group as compared with the control group: 30.0% vs. 6.7% (95% CI: 0.047-0.420; p = 0.045). An additional 8 patients stopped everolimus because of toxicity. At the end of follow-up (month 12) only 12 (40%) patients assigned to everolimus were still on the study drug.

Conclusions: Conversion from tacrolimus to everolimus-based immunosuppression with withdrawal of prednisolone three months after kidney transplantation results in an unacceptably high risk of acute rejection and causes considerable toxicity. Based on our findings, such a switch strategy cannot be recommended.

KEYWORDS

Everolimus, kidney, randomised-controlled trial, tacrolimus, transplantation

INTRODUCTION

Everolimus is an immunosuppressive drug that lacks the chronic nephrotoxic effects of the calcineurin inhibitors (CNIs) tacrolimus and cyclosporine and has the potential to improve long-term outcomes of kidney transplantation.[1,2] In the first clinical trials, everolimus was combined with cyclosporine in *de novo* kidney transplant recipients. These trials did not demonstrate a significant improvement in renal function compared with standard CNI-based immunosuppression. Everolimus was found to have considerable toxicity, including delayed wound healing, the formation of lymphoceles, dyslipidaemia and cytopenia.[2-4] An alternative strategy that has been tested in clinical studies is to convert patients from a CNI-based immunosuppressive regimen to an everolimus-based immunosuppressive regimen longer (i.e. >1 year) after transplantation. The results of these studies have been disappointing as the majority failed to demonstrate a significant improvement in renal function.[5,6]

At present, switching kidney transplant recipients sometime after the critical early post-transplant phase, when rejection risk is highest, from a CNI to everolimus seems to have the most potential in terms of improving

long-term renal transplant function without risking excess acute rejection. In the randomised, controlled ZEUS trial, patients were randomised to either continue cyclosporine or were converted to everolimus 4.5 months after transplantation.[7] This trial demonstrated that conversion to everolimus resulted in superior renal function 1, 3 and 5 years after transplantation, despite a moderately increased risk of acute rejection (13.6% vs. 7.5% after 5 years).[7-9] However, in the ZEUS study, everolimus was compared with a cyclosporine-based immunosuppressive regimen.[7] At present, in most transplant centres in the United States and in Europe, tacrolimus is the cornerstone immunosuppressant. It remains to be determined if switching from tacrolimus to everolimus will result in equally good outcomes and what the optimal timing of such a conversion would be.

The objective of this randomised, controlled clinical trial was to investigate if conversion from a tacrolimus-based immunosuppressive regimen to an everolimus-based regimen at month 3 after living-donor kidney transplantation in low to moderate immunological risk patients with complete and early elimination of glucocorticoids results in an improvement of renal transplant function.

MATERIALS AND METHODS

Study design

This was an investigator-initiated, prospective, randomised, controlled, parallel group, open label, single centre trial that was conducted in the Erasmus MC, University Medical Centre Rotterdam, the Netherlands.

Adult patients (≥ 18 years) who received a blood group AB0-compatible kidney transplant from a living donor (excluding HLA-identical siblings), who were transplanted in our hospital and on continued follow-up in our clinic, were eligible for participation. The patients had to be treated with immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil and prednisolone at month 3 after transplantation. All patients received induction therapy with basiliximab (Simulect®, Novartis Pharma B.V., Arnhem, the Netherlands) in a dose of 20 mg intravenously on days 0 and 4. None of the patients received induction therapy with lymphocyte depleting antibodies.

Exclusion criteria were 1) an acute rejection episode less than 4 weeks prior to the planned randomisation; 2) proteinuria ≥ 1.0 g/day; 3) estimated GFR (eGFR) ≤ 30 ml/min; 4) recipient of multiple organ transplants; 5) a positive pre-transplant complement-dependent cytotoxicity cross-match; 6) human immunodeficiency virus seropositivity; 7) recipients of an allograft from a hepatitis B surface antigen or a hepatitis C virus seropositive donor; 8) severe allergy / hypersensitivity to drugs similar to everolimus (such as macrolides); 9) severe, uncontrollable hypercholesterolaemia or hypertriglyceridaemia; 10) a white blood cell count ≤ 2000/mm^3 or a platelet count ≤ 50,000/mm^3; 11) ongoing wound healing problems; 12) clinically significant infections; 13) severe surgical problems in the opinion of the investigator; 14) intractable immunosuppressant complications or side effects; 15) pregnant or lactating patients; 16) patients who were planning to become pregnant or were unwilling to use effective means of contraception. Donor-specific anti-HLA antibodies were not measured at the time of inclusion (nor thereafter during the course of the trial) and were thus not considered as a possible exclusion criterion.

Interim analyses were planned after the inclusion of 60 patients and again after the inclusion of 120 patients. A data safety monitoring board was instituted to analyse the interim analyses and decide on continuation or modification of the trial.

The study was approved by the institutional review board of the Erasmus MC (Medical Ethical Review Board number 2010-235) and was registered in the Dutch National Trial Registry (http://www.trialregister.nl/trialreg/index.asp; number: NTR2545, registered 6 September 2010). Written informed consent was obtained from all patients before randomisation. The study was performed in compliance with the Good Clinical Practice guidelines and in accordance with the declaration of Helsinki.

Intervention and randomisation

The patients were enrolled and randomised on a 1:1 basis by one of the coordinating investigators (R.B., N.S., T.v.G., or D.A.H.) to either continue tacrolimus or to switch to everolimus-based maintenance immunosuppressive therapy. The randomisation was performed by use of sealed, opaque, sequentially-numbered envelopes containing treatment allocation. The random-allocation sequence was generated by an independent statistician using a random number generator on a computer. Data were collected, monitored and entered by the coordinating investigators and stored in a hospital-based electronic study database.

All patients received tacrolimus (Prograf®, Astellas Pharma, Leiden, the Netherlands), mycophenolate mofetil (Cellcept®, Roche Pharmaceuticals, Basel, Switzerland) and prednisolone triple immunosuppressive therapy at the time of enrolment and randomisation which was month 3 ± 3 weeks. After randomisation, patients either continued treatment with tacrolimus (aiming for pre-dose concentrations of 5-10 ng/ml) or were converted to everolimus (Certican®, Novartis Pharma B.V., Arnhem, the Netherlands) therapy. The everolimus starting dose was 1.5 mg twice daily and thereafter the everolimus dose was

adjusted aiming for whole blood pre-dose concentrations of 4-7 ng/ml. Tacrolimus was reduced to 50% on the day of initiation of the everolimus therapy. One week after the introduction of everolimus, tacrolimus was withdrawn. Following our standard immunosuppressive protocol, prednisolone was tapered from 20 mg orally (started on day 3 after transplantation; all patients received 100 mg prednisolone intravenously for the first 3 days) to 5 mg over the course of the first three postoperative months. Prednisolone was tapered from 5 mg daily at the time of conversion to 0 mg in one month's time following randomisation in both groups. The reason for complete glucocorticoid elimination in both arms was the fact that combination therapy of tacrolimus plus mycophenolate mofetil with complete cessation of glucocorticoids has been the standard of care in our centre for more than 10 years. Continuation of prednisolone in the control arm was therefore considered unethical.

Renal transplant biopsies

All patients included in this trial were asked to undergo a protocol biopsy at month 3 and again at month 12 after transplantation. However, this protocol biopsy was not mandatory and patients could be included in the trial without a baseline protocol biopsy. All biopsies (both for cause and protocol) were assessed locally by two pathologists (M.C.C.-v.G. and J.D.) and scored according to the most recent Banff criteria.[10] For the trial reported here, only renal transplant biopsies to determine cause were considered and analysed.

Endpoints

The primary endpoint of the trial was renal function (eGFR) at month 12 ± 6 weeks after transplantation calculated by the 4-variable MDRD formula.[11] Secondary endpoints were graft survival, the incidence of biopsy-proven acute rejection (BPAR) between month 3 and month 12 (based on for cause biopsy findings only), adverse events (AE), serious adverse events (SAE) and renal histology on protocol biopsy (including signs of CNI-related nephrotoxicity at month 12).

Safety

The incidence of adverse events was registered. An adverse event was defined as serious when 1) it necessitated or prolonged patient hospitalisation; 2) caused persistent or significant disability or incapacity; 3) was life-threatening; 4) caused the death of a patient or 5) required an intervention to prevent an event listed under point 1) to 4). Patients were followed until month 12 ± 6 weeks after transplantation.

Tacrolimus and everolimus concentration measurements

Tacrolimus concentrations were measured in ethylene diamine tetra-acetic acid (EDTA) blood using the affinity chrome-mediated flex-immunoassay (ACMIA) on a Dimension Xpand analyser (Siemens HealthCare Diagnostics Inc., Newark, DE) in accordance with the manufacturer's instructions.[12] Everolimus concentrations were determined using the sirolimus ACMIA kit from Siemens that highly cross-reacts with everolimus.[13]

Statistical analysis

It was estimated that a total of 194 patients had to be included in the trial in order to detect a difference in eGFR of 8 ml/min per 1.73 m^2 between the two groups with a 90% power and accounting for a 30% dropout rate. Because the trial was terminated prematurely (after the first interim analysis), the focus of this report is on the safety aspects of conversion from tacrolimus to everolimus. Data on the primary endpoint (eGFR) will be presented for completeness.

For the analysis, an intention-to-treat approach was followed, which included all randomised patients who received at least one dose of the assigned drug. All summary statistics are presented by treatment group. Frequency distributions are provided for categorical variables. The two treatment groups were compared using χ^2 tests or Student's t test to evaluate the null hypothesis of no difference in eGFR (and the secondary endpoints) between the tacrolimus and everolimus groups. For 2 x 2 tables, Yates' correction for continuity was used. If the minimal expected value in a 2 x 2 table was below 5, Fisher's exact test was used. The Shapiro-Wilk test was used to assess the normality of data. When this assumption was violated, the median and range are displayed and the Mann-Whitney U test was used to evaluate the null hypothesis of no relationship between secondary endpoints. All statistical tests were two-sided and used the 0.05 level of statistical significance. The statistical analyses were conducted using IBM SPSS Statistics version 21.0. Armonk, NY: IBM Corp.

Role of the funder

This was an investigator-initiated study. The trial was financially supported by Novartis Pharma B.V., Arnhem, the Netherlands, the producer of everolimus. Novartis Pharma B.V. had no role in the study design, data collection, data analyses, data interpretation, or writing of the report. All authors had full access to all the data, had final responsibility for the contents of this publication and the decision to submit for publication.

RESULTS

Patient population and trial progress

This study was conducted between 17 February 2011 (first patient, first visit) and 14 March 2014 (last patient, last visit). A total of 457 patients were screened for participation in the trial of which 136 were eligible, as shown in *figure 1*. Sixty patients gave written informed consent and were subsequently included and randomised. The characteristics of these 60 patients are summarised in *table 1*. Patients were enrolled in the study at a median of 96 days (range 83-111) after transplantation. A total of 58 patients (96.7%) completed the 9 month (± 6 weeks) follow-up. At the end of follow-up, 100% in the control group were on the assigned therapy, while only 40% of the patients in the intervention group were still on everolimus ($p < 0.001$). The primary reasons for discontinuing everolimus were acute rejection (number in group (n) = 9) and toxicity (n = 8); see *figure 1* and below.

The trial was ended prematurely after the first, pre-planned interim analysis. The reasons for discontinuation were twofold. First, the interim analysis showed a significantly and unacceptably high incidence of BPAR in the everolimus group compared with the tacrolimus group: 30.0% vs. 6.7%; $p = 0.042$ (*figure 2*) (for details see below: under 'Acute rejection'). Second, because the clinical condition of these patients required re-conversion to tacrolimus and because a considerable number of non-rejecting patients stopped taking everolimus for other reasons (see below), the overall dropout rate was 60%, which was much higher than the anticipated 30%.

Acute rejection

Overall, the BPAR rate in the everolimus group was 30.0% vs. 6.7% in the control group (95% CI: 0.048; 0.420; $p = 0.045$) (*figure 2*). Banff grades and frequencies are depicted in *table 2*. No cases of presumed acute rejection (i.e. clinically suspected rejection without histological confirmation) occurred. Baseline characteristics between rejectors and non-rejectors in the everolimus group are listed in *Supplementary table 1*. Estimated GFR at month 3 (baseline) was significantly lower among rejectors ($U = 59.5$; $p = 0.04$). There were no significant differences in everolimus dosages and concentration measurements between rejectors and non-rejectors.

Safety and tolerability

One patient (randomised to tacrolimus) died 272 days after transplantation due to metastasised gastric carcinoma.

Figure 1. *Trial flowchart (all patients randomised received at least one dose of the assigned drug)*

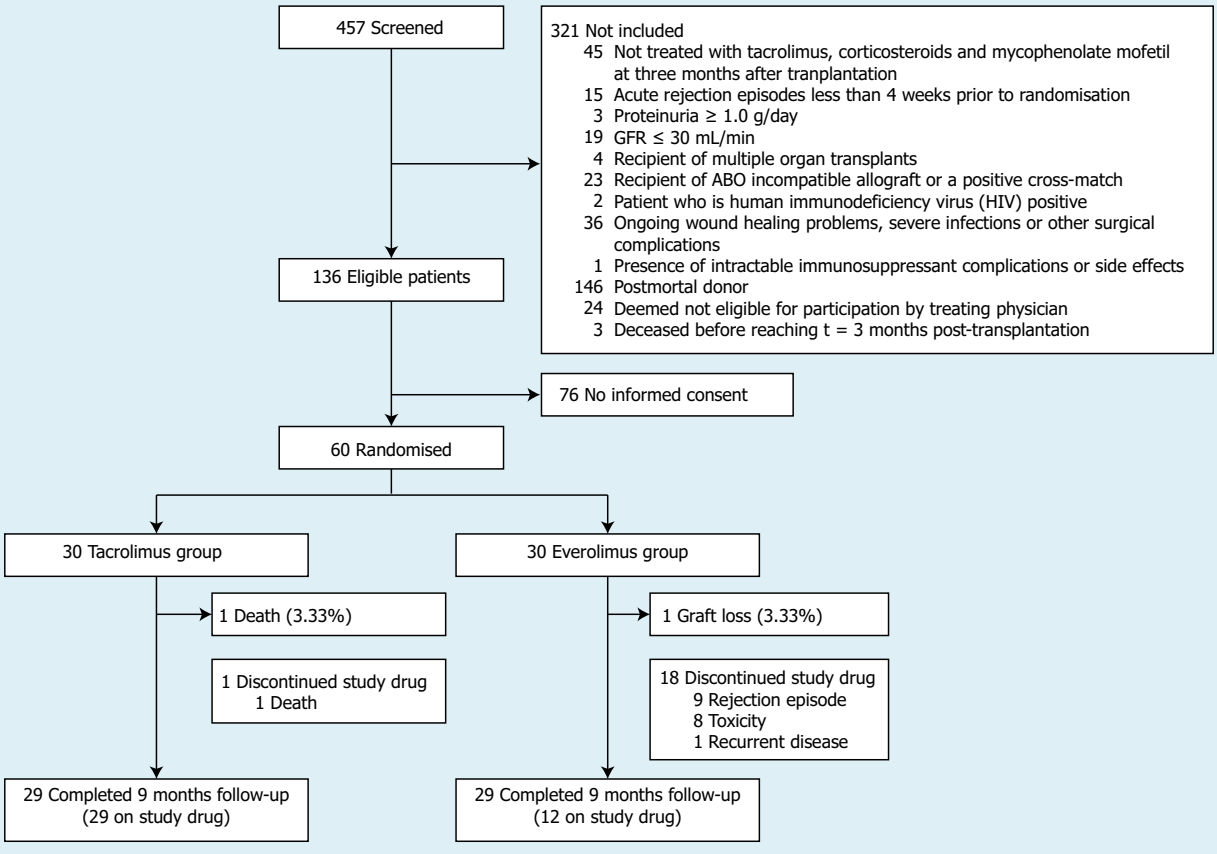
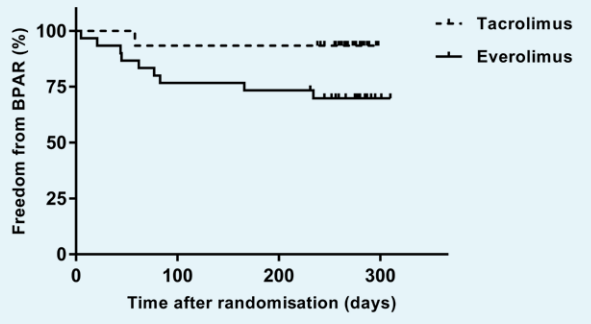


Figure 2. *Cumulative survival curve of non-rejectors*



This resulted in a patient survival of 97% and 100%, in the tacrolimus and everolimus groups, respectively (p = 0.41). One patient (randomised to everolimus) lost his graft as a result of uncontrollable acute rejection.

The AEs are listed in *table 3*. A total of 406 adverse events were observed. Of these, n = 52 (12.8 %) were considered severe. A total of 238 vs. 168 AEs occurred in the everolimus and tacrolimus group, respectively (χ^2 (1df) = 12,069; p = 0.001). There was no difference in the incidence of SAEs in the everolimus and tacrolimus group: 25 vs. 26 (χ^2 (1df) = 0.020; p = 0.89). Peripheral oedema and oral ulcers occurred more frequently among everolimus-treated patients. The incidence of all other AEs was not significantly different between the two groups.

A dropout rate of 60% (n = 18) was observed in the everolimus group. Of the patients, 30% were reconverted to tacrolimus because of acute rejection (n = 9). Another 26.7% were reconverted because of toxicity (n = 8). Of these eight patients, three were reconverted to tacrolimus because of severe peripheral oedema, one because of peripheral oedema in combination with leucopenia and exanthema, one because of oral ulcers and peripheral oedema, one because of exanthema, one because of pancytopenia, and in one case due to severe pneumonitis. One other patient was reconverted to tacrolimus because of the recurrence of his primary kidney disease (granulomatosis with polyangiitis).

Table 1. *Baseline characteristics*

	Tacrolimus group (n = 30)	Everolimus group (n = 30)
Age at time of transplant (years)	56 (11)	51 (15)
Gender		
- Male/female	25 (83%) / 5 (17%)	19 (63%) / 11 (37%)
Ethnicity		
- White	26 (87%)	25 (83%)
- Black	1 (3%)	2 (7%)
- Asian	0	2 (7%)
- Other	3 (10%)	1 (3%)
BMI (kg/m^2)	27.2 (3.6)	26.7 (3.5)
Number of kidney transplantation		
- 1st	30 (100%)	26 (87%)
- 2nd	0	4 (13%)
Primary kidney disease		
- Hypertensive nephropathy	8 (27%)	5 (17%)
- Diabetic nephropathy	5 (17%)	4 (13%)
- Polycystic kidney disease	5 (17%)	4 (13%)
- Glomerulonephritis	4 (13%)	9 (30%)
- Reflux disease / Chronic pyelonephritis	3 (10%)	2 (7%)
- Other	2 (7%)	4 (13%)
- Unknown	3 (10%)	2 (7%)
Donor type		
Living-related/Living-unrelated	10 (33%) / 20 (67%)	14 (47%) / 16 (53%)
- PRA % (< 15% / ≥ 15%)	30 (100%) / 0 (0%)	27 (90%) / 3 (10%)
- Peak PRA % (< 15% / ≥ 15%)	29 (97%) / 1 (3%)	25 (83%) / 5 (17%)
- HLA mismatches	3.4 (1.2)	3.5 (1.5)

Data represents mean (SD) or n (%). PRA = panel reactive antibodies.

Primary endpoint

At month 12 after transplantation, there was no statistically significant difference with regard to eGFR between the tacrolimus and everolimus group: 53 vs. 56 ml/min per 1.73 m^2, respectively (p = 0.52). The difference at month 12 was 3 ml/min per 1.73 m^2. In the tacrolimus group an average decrease of Δ = -1 ml/min in eGFR occurred over the course of 9 months, whereas in the everolimus group an increase of Δ = 2 ml/min occurred during this same period. Median protein/creatinine ratios were significantly different between the everolimus and tacrolimus group: 18.7 vs. 11.8 mg/mmol, respectively (U = 212.5; p = 0.005; *table 4*).

Secondary outcomes

The outcome parameters are listed in *table 4*. At baseline, no significant differences between efficacy parameters were found. Differences per group between month 3 and month 12 are shown in *Supplementary table 2*.

At month 12 there was a significant difference in haemoglobin concentration in favour of the tacrolimus

Table 2. *Incidence of biopsy-proven acute rejection*

	Tacrolimus group	Everolimus group
	(n = 30)	(n = 30)
Borderline	0 (0.0%)	0 (0.0%)
Type 1		
- 1A	0 (0.0%)	2 (6.7%)
- 1B	0 (0.0%)	2 (6.7%)
Type 2		
- 2A	1 (3.3%)	2 (6.7%)
- 2B	0 (0.0%)	1 (3.3%)
Type 3	1 (3.3%)	0 (0.0%)
ABMR	0 (0.0%)	1 (3.3%)
Mixed ACR and ABMR	0 (0.0%)	1 (3.3%)
Total	**2 (6.7%)**	**9 (30.0%)**

ABMR = antibody mediated rejection; ACR = acute cellular rejection.

Table 3. *Adverse events*

Event	Tacrolimus group (n = 30)	Everolimus group (n = 30)	p
Blood or lymphatic system	11	28	0.12
- Leucopenia	8	19	
- Anaemia	2	5	
- Thrombocytopenia	0	2	
- Other	1	2	
Bleeding and thrombotic events	4	3	0.45
- Thrombotic event	2	2	
- Bleeding	2	1	
Malignancy	1	1	> 0.99
Cardiac	4	6	> 0.99
- Cardiac decompensation	1	3	
- Other	3	3	
Gastrointestinal	18	13	0.07
- Diarrhoea	8	4	
- Other	10	9	
Oral ulcer	0	9	0.01
Opportunistic infection	5	13	0.35
- Cytomegalovirus	2	4	
- Herpes simplex virus	2	4	
- BK viraemia	1	3	
- Epstein-Barr virus	0	2	
Other infection	34	44	0.73
- Respiratory tract infection	11	18	
- Urinary tract infection	9	6	
- Gastroenteritis	8	4	
- Other	6	16	
Locomotor system disorder	17	13	0.11
Metabolism or nutrition	8	9	0.81
- Liver enzyme abnormality	1	5	
- Dysregulation of pre-existing DM	5	3	
- Post-transplant DM	2	1	
Nervous system	6	12	0.65
- Headache	2	4	
- Tremor	1	3	
- Other	3	5	
Skin-related disorders	3	14	0.08
- Maculopapular rash	0	8	
- Other	3	6	
Tacrolimus-induced nephrotoxicity	2	0	0.17
Urological complication	5	2	0.13
Wound-related problem	2	2	> 0.99
Other	24	33	> 0.99
Allergic reaction	0	1	> 0.99
Other laboratory abnormality	19	17	0.20
- Hypovitaminosis D	6	6	
- Iron deficiency	5	5	
- Hypercalcaemia	4	1	
- Hypophosphataemia	1	3	
- Other	3	2	
(Peripheral) oedema	4	18	0.04
Total	**167**	**238**	

vervolg **Table 3.** *Adverse events*

DM = diabetes mellitus.

Table 4. *Outcome parameters*

	Month 12				
	n	**Tacrolimus group**	**n**	**Everolimus group**	**p (CI) / p (U)***
Body weight (kg)	25	86.8 (67.5; 109.2)	26	82.4 (53; 143.5)	0.11 (239.0)
BMI (kg/m²)		26 (6)		26 (7)	0.73 (-2.89; 4.13)
Blood pressure					
Systolic/diastolic (mmHg)	25	138 (15) / 81 (11)	25	132 (13) / 79 (9)	0.17 (-2.41; 13.37) / 0.58 (-4.19; 7.39)
Kidney function					
Creatinine (µmol/l)	29	121 (66; 190)	29	108 (58; 238)	0.20 (338.5)
eGFR (ml/min per 1.73 m²)	29	53 (13)	29	56 (18)	0.52 (-11.07; 5.69)
Protein/creatinine ratio	29	11.8 (2.0; 59.6)	27	18.7 (5.7; 296.1)	0.01 (212.5)
Glucose metabolism					
Glucose (mmol/l)	27	6.2 (3.9; 16.8)	27	5.4 (4.0; 8.8)	0.14 (279.5)
HbA1c (mmol/mol)	20	42.0 (3.6; 93.0)	17	40.0 (31.0; 46.0)	0.21 (129.0)
Lipids					
Cholesterol, total (mmol/l)	25	4.2 (1.0)	24	5.0 (1.2)	0.01 (-1.44; -0.21)
Triglycerides (mmol/l)	25	1.5 (0.6; 3.9)	24	1.7 (0.5; 7.0)	0.29 (247.5)
HDL-cholesterol (mmol/l)	25	1.3 (0.3)	24	1.4 (0.5)	0.43 (-0.33; 0.14)
LDL-cholesterol (mmol/l)	25	2.4 (0.8)	24	3.0 (0.9)	0.02 (-1.06; -0.85)
Haematology					
Haemoglobin (mmol/l)	27	8.7 (0.7)	29	7.8 (1.0)	<0.001 (0.47; 1.41)
MCV (fl)	27	86 (5)	29	85 (5)	0.20 (-0.96; 4.52)
Thrombocytes (×10^9/l)	27	230 (129; 806)	29	231 (124; 436)	0.90 (384.0)
Leucocytes (×10^9/l)	27	6.8 (3.4; 14.8)	29	6.6 (3.2; 17.4)	0.75 (372.0)

*Data represents mean (SD) and p (Confidence interval of the difference of the mean) or median (range) and p (U). eGFR = estimated GFR; MCV = mean corpuscular volume.

group. When adjusted for gender and baseline haemoglobin, the difference between groups remained statistically significantly different ($p < 0.001$). Total cholesterol level and LDL cholesterol were significantly lower in the tacrolimus group at month 12. All other outcome parameters were not significantly different between the two groups (*table 4*).

Medication dosages and changes are listed in *Supplementary table 3*. There were no significant changes in medication usage between groups at month 12. Increased use of antihypertensive and lipid-lowering drugs as compared with baseline was observed in both groups. There were no statistically significant changes in the use of glucose-lowering drugs.

DISCUSSION

Conversion from tacrolimus to everolimus-based immunosuppression three months after transplantation with complete and early withdrawal of glucocorticoids is not safe in living-donor kidney transplant recipients. Conversion results in an unacceptably high risk of acute rejection. Moreover, a considerable number of patients discontinued everolimus because of side effects.

The results of this trial differ from other randomised trials that studied early conversion from a CNI-based to an everolimus-based immunosuppressive regimen.[14,15] The investigators of the ZEUS trial concluded that early conversion (month 4.5 after transplantation)

from cyclosporine to everolimus resulted in improved kidney function without compromising efficacy and safety.[14] In the Dutch multi-centre MECANO trial, renal transplant recipients were converted from cyclosporine, mycophenolate sodium and prednisolone-based immunosuppression to everolimus/prednisolone or cyclosporine/prednisolone combination therapy at month 6 after transplantation. Conversion to everolimus-based immunosuppression resulted in better renal function and better preservation of renal histology compared with patients who were treated with cyclosporine/prednisolone-based therapy.[15]

In the ELEVATE trial, 715 *de novo* kidney transplant recipients were randomised at 10-14 weeks to convert to everolimus (n = 359) or remain on standard CNI therapy [n = 356; tacrolimus (n = 231) or cyclosporine (n = 125)] in combination with mycophenolic acid and glucocorticoids.[16] In ELEVATE, there was no difference in the primary endpoint, the estimated change in eGFR from randomisation to month 12 post-transplant.[16] In line with the observations made in the present trial, in ELEVATE the incidence of BPAR in the everolimus arm (9.7%) was comparable with that of patients who remained on cyclosporine (8.8%) but was significantly higher compared with patients who continued tacrolimus-based immunosuppression (2.6%).[16]

A major difference between the present study and previous investigations is the complete cessation of glucocorticoids after conversion to everolimus. We chose to eliminate prednisolone in both groups because double immunosuppressive therapy consisting of tacrolimus and mycophenolate mofetil (from month 4 onwards) is standard practice in our centre. In the ZEUS and ELEVATE trials, patients were maintained on ≥ 5 mg of prednisolone (or an equivalent glucocorticoid).[14,16] Another difference between the present study and previous investigations was the type of CNI in the control group. In the ELEVATE trial, patients were converted to everolimus from either tacrolimus or cyclosporine, whereas in the ZEUS trial all patients were on cyclosporine at baseline.[7,14,16] In the trial reported here, all patients were treated with tacrolimus, which is considered more potent compared with cyclosporine.[17]

High rates of acute rejection were also observed in other trials in which patients were converted from a CNI to everolimus.[7,14,18-20] In the CENTRAL study, 27.5% of the patients randomised from cyclosporine/tacrolimus to everolimus experienced an episode of acute rejection in the first year. CENTRAL had a similar design as the trial reported here, except that the conversion was performed as early as 7 weeks after transplantation.[19]

Drop out in the everolimus group was high. In 30% of patients, everolimus was stopped because of rejection, whereas in another 26.7% of patients, everolimus was stopped because of toxicity. In most cases, these were typical side effects associated with the use of an mTOR inhibitor, such as oedema and exanthema. Management of side effects was left to the attending physician but an effort was made to keep patients on their assigned treatment. In general, if possible, a dose reduction of everolimus was performed and any concomitant medication (such as co-trimoxazole, valganciclovir, or calcium channel blockers) was first withdrawn or reduced if this was considered the cause of the symptoms. Oral ulcers were often managed with topical steroids. However, several patients requested conversion to tacrolimus and refused further treatment with everolimus when these troublesome side effects occurred.

The high dropout rate because of everolimus-related side effects is consistent with results of other switch studies. However, there is a big difference in discontinuation of everolimus because of toxicity in the first year between studies (12.5%-32.6%).[5,6,14-16,19,20] The CENTRAL study investigators reported a 43.1% dropout in the everolimus group in the first year. Of the 43.1% dropout, toxicity accounted for 25.5%, rejection for 13.7%, and other reasons for 3.9%.[19] In the ZEUS study, dropout because of toxicity and rejection was 6.5% and 3.9%, respectively, after 1 year in the everolimus group.[7] However, 10% of the patients assigned to everolimus experienced an episode of BPAR, indicating that physicians were less inclined to switch back to a CNI, even when treatment with everolimus was failing.[7] The willingness of treating physicians to switch back to a CNI after a period of rejection or adverse events may contribute greatly to the differences in dropout observed between studies.

No difference in the primary endpoint was observed between the two groups. At month 12, renal function was comparable between the two groups. Obviously, the present study – which only included a limited number of patients – was not powered to detect such a difference. However, we think it unlikely that any such difference would have been detected if the planned 194 patients had been included. Any benefit of everolimus in terms of improved renal function, as has been reported previously,[7-9,15] would likely have been offset by the higher rejection risk. Results from the on-treatment analysis (n = 12; *Supplementary table 4*) showed a significantly improved kidney function in the group which was switched and continued everolimus vs. those who remained on tacrolimus (eGFR of 66 vs. 53 ml/min, p = 0.01). Thus, a proportion of patients seem to benefit from conversion to everolimus in terms of improved renal function. However, whether this benefit persists over time remains to be determined. Of note, in a long-term follow-up study, patients randomised to everolimus were found to more often develop *de novo* donor-specific anti-HLA antibodies which is considered a risk factor for chronic rejection.[21] Furthermore, there are at present no reliable biomarkers that can assist clinicians in identifying patients who will do well after conversion from a CNI to everolimus.[2,22]

Our study has several limitations; the trial was ended prematurely which resulted in a small number of patients available for the analysis. The study therefore lacks the power to detect significant differences in the primary endpoint and the small number of patients increases the probability of detecting a difference by chance (type 1 statistical error). However, the significant difference in the incidence of BPAR is in line with other studies and we feel that these results are not random. Second, our population primarily consisted of Caucasian males, making the results not generalisable to all patient populations. Still, as African American transplant recipients are considered high-immunological risk patients, also for this patient group conversion to everolimus may not be advisable.[23] Finally, as mentioned above, complete and early cessation of glucocorticoids after month 3 is not standard practice in many transplant centres.

The publication of results of studies that are stopped prematurely is very important.[24] These publications provide important information for researchers who are considering to embark on studies with similar goals and study designs. Furthermore, for systematic reviews with meta-analysis, a balanced representation in the literature of studies with positive and negative outcome results is crucial.[25]

In summary, conversion from tacrolimus to everolimus-based immunosuppression with compete withdrawal of prednisolone three months after living-donor kidney transplantation results in an unacceptably high risk of acute rejection in addition to causing considerable toxicity. Based on the present findings, such a switch strategy should not be considered safe and cannot be recommended.

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APPENDIX

Table S1. *Baseline characteristics everolimus group: non-rejectors vs. rejectors*

	n	Non-rejectors (n = 19)	n	Rejectors (n = 9)	p (CI) / p (U)
BMI (kg/m²)	19	26.9 (3.6)	9	26.4 (3.5)	0.78 (-2.6; 3.4)
Blood pressure					
Systolic (mmHg)	20	136 (18)	9	138(17)	0.88 (-15.6; 13.3)
Diastolic (mmHg)	20	75 (65; 110)	9	80 (70; 101)	0.71 (82.0)
Kidney function					
Creatinine (µmol/l)	21	114 (32)	9	145 (35)	0.03 (-57.1; -4.2)
eGFR (ml/min per 1.73 m²)	21	53 (35; 90)	9	41 (32; 77)	0.04 (59.5)
Protein/creatinine ratio (mg/mmol)	20	16.5 (3.6; 77.0)	8	18.9 (8.2; 53.1)	0.54 (68.0)
Glucose metabolism					
Glucose (mmol/l)	20	5.9 (4.2; 10.0)	9	5.6 (5.0; 9.0)	0.83 (85.5)
HbA1c (mmol/mol)	12	40 (39; 62)	4	40 (33; 46)	0.58 (19.5)
Lipids					
Cholesterol total (mmol/l)	18	5.2 (1.2)	6	5.0 (0.8)	0.67 (-0.8; 1.3)
Triglycerides (mmol/l)	18	1.9 (0.9)	6	1.2 (0.4)	0.02 (0.1; 1.2)
HDL-cholesterol (mmol/l)	18	1.39 (0.82; 3.00)	6	1.60 (0.91; 1.95)	0.42 (42.0)
LDL-cholesterol (mmol/l)	18	3.2 (1.1)	6	3.1 (0.7)	0.79 (-0.9; 1.1)
Haematology					
Haemoglobin (mmol/l)	21	7.5 (1.0)	8	7.6 (1.3)	0.75 (-1.1; 0.8)
MCV (fL)	21	91 (4)	9	88 (5)	0.21 (-1.5; 6.3)
Thrombocytes (×10^9/l)	21	271 (79)	9	237 (63)	0.26 (-26.9; 95.0)
Leucocytes (×10^9/l)	21	6.9 (2.8)	9	6.8 (3.1)	0.95 (-2.3; 2.4)
Medication					
Everolimus dose (mg/day)*	21	1.83 (0.83)	9	1.77 (0.91)	0.87 (-0.78; 0.67)
Everolimus predose concentration (ng/ml)*	21	5.8 (1.7)	9	6.2 (2.6)	0.66 (-1.50; 2.34)

Data represents mean (SD) and p (CI) or median (range) and p (U) *Measured at time of rejection. Non rejectors whole blood concentration was measured at month 12 or, when reconverted to tacrolimus for another reason, last concentration before reintroduction of tacrolimus.

Table S2. *Per group changes between month 3 and 12*

	Tacrolimus	Everolimus	n	p (CI) / p (U)
Δ BMI (kg/m²)	0.5 (1.5)	-0.1 (1.5)	50	0.20 (-0.3; 1.4)
Δ Blood pressure				
Systolic (mmHg)	2.4 (18.7)	-3.7 (20.0)	47	0.29 (-5.3; 17.5)
Diastolic (mmHg)	1.2 (10.3)	-1.0 (12.6)	58	0.47 (-3.8; 8.2)
Δ Kidney function				
Creatinine (µmol/l)	2 (-25; 34)	-3 (-47; 93)	58	0.50 (377.5)
eGFR (ml/min)	-0.1 (11.4)	1.3 (9.2)	58	0.61 (-6.9; 4.1)
Protein/creatinine ratio (mg/mmol)	-2.1 (-37.1; 19.6)	3.1 (-36.7; 280.7)	54	0.23 (295.0)
Δ Glucose metabolism				
Glucose (mmol/l)	0.0 (2.2)	-0.4 (1.3)	48	0.47 (-0.7; 1.4)
HbA1c (mmol/mol)	-0.7 (7.0)	-2.7 (4.9)	19	0.49 (-3.9; 7.9)
Δ Lipids*				
Cholesterol total (mmol/l)	-0.7 (1.9)	0.0 (1.3)	36	0.23 (-1.8; 0.4)
Triglycerides (mmol/l)	-0.6 (-2.9; 0.9)	0.2 (-0.6; 5.3)	36	0.01 (79.0)
HDL-cholesterol (mmol/l)	-0.1 (-0.5; 1.5)	-0.2 (-1.0; 1.3)	36	0.28 (128.0)
LDL-cholesterol (mmol/l)	-0.5 (1.4)	0.0 (1.1)	36	0.26 (-1.3; 0.4)
Δ Haematology				
Haemoglobin (mmol/l)	0.8 (-0.4; 3.1)	0.3 (-1.7; 3.5)	56	0.01 (227.0)
MCV (fl)	-3 (-9; 7)	-6 (-18; 8)	56	< 0.01 (217.5)
Thrombocytes (×10^9/l)	-30 (53)	-16 (59)	56	0.35 (-44; 16)
Leucocytes (×10^9/l)	0.16 (2.33)	0.11 (3.33)	56	0.95 (-1.50; 1.60)

Data is mean (SD) and p (CI) or median (range) and p (U); eGFR = estimated glomerular filtration rate; MCV = mean corpuscular volume.

Table S3. *Medication dosages*

Medicine	Tacrolimus group	Everolimus Group	p
Month 3 (n)	30	30	
Month 12 (n)	29	29	
Tacrolimus dose (mg/day)			
Month 3	5.6 (3.0)	5.4 (2.3)	
Month 12	4.0 (2.3)	4.3 (2.1)[1]	0.69
Tacrolimus predose concentration (ng/ml)			
Month 3	7.4 (1.8)	8.4 (3.1)	
Month 12	6.6 (2.9)	7.1 (5.1)[1]	0.72
Everolimus dose (mg/day)	-	1.48 (0.45)[2]	
Everolimus predose concentration (ng/ml)	-	5.5 (1.7)[3]	
MMF dose (mg/day)			
Month 3	1367 (706)	1283 (520)	
Month 12	1092 (438)	966 (325)	0.22
MPA predose concentration (mg/l)			
Month 3	2.4 (1.9)	2.6 (1.1)	
Month 12	1.5 (0.6)	1.7 (0.9)	0.25
Antihypertensive drugs (mean (SD))			**0.59**
Decreased drug use	5 (17%)	4 (13%)	
Same drug use	13 (43%)	17 (57%)	
Increased drug use	12 (40%)	9 (30%)	
Glucose-lowering drugs (mean (SD))			**0.23**
Decreased drug use	4 (13%)	2 (7%)	
Same drug use	24 (80%)	28 (93%)	
Increased drug use	2 (7%)	0 (0%)	
Lipid-lowering drugs (mean (SD))			**0.32**
Decreased drug use	2 (7%)	0 (0%)	
Same drug use	22 (73%)	25 (83%)	
Increased drug use	6 (20%)	5 (17%)	

Data represents mean (SD) or n (% of the group); MMF =mycophenolate mofetil; MPA = mycophenolic acid. [1]Patients re-converted to tacrolimus, n = 17; [2]n = 12; [3]n = 11, in one patient assigned to everolimus, the concentration measurement was missing.

Table S4. *On treatment analysis*

	Month 12				
	Tacrolimus		Everolimus		p (CI) / p (U)
	n	n = 29	n	n = 12	
BMI (kg/m²)	25	27.5 (21.6; 34.6)	10	25.9 (24.1; 34.0)	0.65 (112.5)
Blood pressure					
Systolic (mmHg)	25	138 (15)	10	130 (10)	0.13 (-2.5; 18.3)
Diastolic (mmHg)	25	81 (11)	10	76 (9)	0.26 (-3.5; 12.6)
Kidney function					
Creatinine (µmol/l)	29	125 (31)	12	99 (22)	0.01 (5.6; 45.3)
eGFR (ml/min)	29	53 (13)	12	66 (15)	0.01 (-22.3; -3.4)
Protein/creatinine ratio	28	11.9 (2.0; 59.6)	12	18 (6.3; 95.1)	0.02 (88.5)
Glucose metabolism					
Glucose (mmol/l)	27	6.2 (3.9; 16.8)	11	5.3 (4.4; 8.3)	0.48 (126.5)
HbA1c (mmol/mol)	20	42 (33; 93)	6	39 (31; 42)	0.22 (40.0)
Lipids					
Cholesterol total (mmol/l)	25	4.3 (1.0)	11	5.1 (0.8)	0.02 (-1.5; -0.2)
Triglycerides (mmol/l)	25	1.5 (0.6; 3.9)	11	1.9 (0.5; 7.0)	0.15 (96)
HDL-cholesterol (mmol/l)	25	1.21 (0.80; 2.09)	11	1.09 (0.69; 2.03)	0.31 (108.0)
LDL-cholesterol (mmol/l)	25	2.44 (0.77)	11	3.13 (0.75)	0.02 (-1.3; -0.1)
Haematology					
Haemoglobin (mmol/l)	27	8.7 (0.7)	12	7.5 (0.9)	< 0.01 (0.7; 1.8)
MCV (fL)	27	86 (5)	12	81 (3)	< 0.01 (1.9; 8.5)
Thrombocytes (×10^9/l)	27	230 (129; 806)	12	267 (171; 436)	0.64 (146.5)
Leucocytes (×10^9/l)	27	6.8 (3.4; 14.8)	12	5.8 (3.9; 8.4)	0.22 (122.0)

Data is mean (SD) and p (CI) or median (range) and p (U).

ORIGINAL ARTICLE

Addition of simethicone improves small bowel capsule endoscopy visualisation quality

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ABSTRACT

Background: Small bowel capsule endoscopy (SBCE) is an important diagnostic tool for small-bowel diseases but its quality may be hampered by intraluminal gas. This study evaluated the added value of the anti-foaming agent, simethicone, to a bowel preparation with polyethylene glycol (PEG) on the quality of small bowel visualisation and its use in the Netherlands.

Methods: This was a retrospective, single-blind, cohort study. Patients in the PEG group only received PEG prior to SBCE. Patients in the PEG-S group ingested additional simethicone. Two investigators assessed the quality of small-bowel visualisation using a four-point scale for 'intraluminal gas' and 'faecal contamination'. By means of a survey, the use of anti-foaming agents was assessed in a random sample of 16 Dutch hospitals performing SBCE.

Results: The quality of small bowel visualisation in the PEG group (n = 33) was significantly more limited by intraluminal gas when compared with the PEG-S group (n = 31): proximal segment 83.3% in PEG group vs. 18.5% in PEG-S group ($p < 0.01$), distal segment 66.7% vs. 18.5% respectively ($p < 0.01$). No difference was observed in the amount of faecal contamination (proximal segment 80.0% PEG vs. 59.3% PEG-S, $p = 0.2$; distal segment 90.0% PEG vs. 85.2% PEG-S, $p = 0.7$), mean small bowel transit times (4.0 PEG vs. 3.9 hours PEG-S, $p = 0.7$) and diagnostic yield (43.3% PEG vs. 22.2% PEG-S, $p = 0.16$). Frequency of anti-foaming agent use in the Netherlands was low (3/16, 18.8%).

Conclusion: Simethicone is of added value to a PEG bowel preparation in improving the quality of visualisation of the small bowel by reducing intraluminal gas. At present, the use of anti-foaming agents in SBCE preparation is not standard practice in the Netherlands.

KEYWORDS

Bowel preparation; capsule endoscopy; simethicone; standard of care; visualisation quality

INTRODUCTION

Small bowel capsule endoscopy (SBCE) has proven to play a crucial role in the diagnosis and management of several small-bowel diseases such as obscure gastrointestinal bleeding and Crohn's disease.[1-4] Unfortunately, its diagnostic yield may be limited by impaired small bowel visualisation quality due to intestinal juice, air bubbles or food residue and a lower completion rate of the examination caused by delayed gastric and small bowel transit time.

A bowel preparation regimen prior to SBCE might improve the quality of small bowel visualisation and thereby the diagnostic yield, but it may also have an adverse effect on gastric and small bowel transit time.[5-7] Since the introduction of SBCE in 2000 a lot of research has been carried out in order to define the optimal preparation regimen prior to SBCE including polyethylene glycol (PEG) and the addition of anti-foaming agents or prokinetics. PEG showed to have a beneficial effect on small bowel visualisation compared with other purgatives.[5,6,8,9] The addition of prokinetics mainly resulted in a shortening of gastric transit time while few effects on small bowel transit time and completion rate were seen.[7,11] Addition of simethicone, an anti-foaming agent, to a preparation of PEG prior to SBCE showed improvement of bowel cleansing and small bowel visualisation in many cases; however, the effect on transit times, diagnostic yield and completion rate remains somewhat contradictory.[12-17] Despite much research regarding the optimal preparation regimen prior to SBCE, no consensus has been reached.[18,19] Differences in the preparation regimens used lead to

heterogeneity. Moreover, no widely accepted measuring method and definition is available of adequate quality of small bowel visualisation, impeding standardisation of an effective bowel preparation regimen.
The primary aim of this study was to evaluate the added value of simethicone to SBCE preparation with PEG on small bowel visualisation quality. We hypothesise that a preparation including simethicone will lead to better small bowel visualisation compared with a preparation of PEG alone. The secondary aim was to evaluate the use of anti-foaming agents for SBCE preparation in the Netherlands.

MATERIALS AND METHODS

Study design and patients

In this single-blinded, retrospective cohort study, data were prospectively collected from patients who underwent SBCE from May 2011 until December 2012.
Exclusion criteria consisted of general contraindications for SBCE such as swallowing difficulties, known or suspected intestinal fistulas or stenosis and the presence of an implantable cardioverter defibrillator. Additional exclusion criteria were impaired intestinal motility, severe diverticulosis, pregnancy and age less than 18 years.

Bowel preparation and SBCE examination

Data on the two cohorts were collected from medical records. One cohort received a preparation with only PEG while the other cohort received PEG and simethicone prior to SBCE. Patients in the PEG group underwent SBCE before November 2012 and received standard bowel preparation consisting of a liquid diet 1 day before SBCE, 2 litres of PEG and a clear liquid diet in the evening before SBCE followed by an overnight fast. Patients in the PEG-S group, who underwent SBCE between March and December 2012, received simethicone in addition to standard bowel preparation with PEG. They ingested 2 ml of simethicone suspension containing a total amount of 82.4 mg of simethicone (Lefax, Bayer, Germany) with a small amount of tap water 15 minutes prior to SBCE. All patients who took iron supplements were asked to temporarily stop these seven days before SBCE.
SBCE was performed using the Pillcam SB (Given Imaging, Israel). All patients were allowed to drink clear liquids and eat a light meal 4 and 6 hours, respectively, after swallowing the capsule. Images were collected for a period of 8 hours until the battery ran out. Images were reviewed using RAPID 4.0 (MedTronic, United States).

Assessment of outcomes

Thirteen out of the total 64 videos were reviewed by two experienced investigators (D.D., S.B.) regarding evaluation of the quality of small bowel visualisation. Interobserver variability was assessed and after agreement was reached on any discrepancies, the other 51 videos were reviewed by only one investigator. In cases of disagreement, investigators discussed the video until consensus was reached. Investigators were blinded to which bowel preparation patients received prior to SBCE. All images of the videos were evaluated by the investigators.
To evaluate small bowel visualisation, the amount of intraluminal gas as well as faecal contamination limiting mucosal visibility was assessed for every video using a four-point grading scale: Grade 0: no intraluminal gas/faecal contamination, Grade 1: a few gas bubbles/little faecal contamination, no limitations for interpretation of SBCE, Grade 2: presence of some intraluminal gas/faecal contamination leading to moderate limitations for interpretation, Grade 3: presence of a substantial amount of intraluminal gas/faecal contamination leading to severe limitations for interpretation. Grade 0 and 1 were classified as not limiting for interpretation of SBCE whereas grade 2 and 3 were considered as limiting for the interpretation of SBCE. The quality of visualisation of the proximal and distal small bowel was assessed separately. The proximal part of the small bowel was defined as one hour of video after the first duodenal bulb image while the distal part of the small bowel began one hour before the first caecal image.
Small bowel transit time was defined as the time from the first image of the duodenal bulb until the first caecal image.
The diagnostic yield was classified as either 'explanatory' or 'not explanatory'. If findings on images could explain the patient's signs or symptoms, diagnostic yield was assessed as 'explanatory'. Images were assessed as 'not explanatory' if they did not show any abnormalities.

Use of anti-foaming agents in the Netherlands

We randomly selected 16 Dutch hospitals who perform SBCE. Selected hospitals were spread over all regions of the Netherlands and consisted of a mix of university hospitals, regional teaching hospitals and peripheral hospitals.
To obtain information on the frequency of the use of an anti-foaming agent prior to SBCE in these hospitals, brochures were consulted and endoscopy departments were contacted by telephone. For this study, we focused on the use of an anti-foaming agent only. Use of purgatives was not included in our analysis.

Statistical analysis

Descriptive statistics were expressed in means ± standard deviation (SD). Differences in categorical variables between patient groups were compared with the chi-square test, differences in means were compared with the unpaired T-test. A p-value <0.05 was considered to be statistically

significant. Statistical analysis was performed using SPSS Statistics software version 22.0 (IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

Data of 64 patients who underwent SBCE were analysed. Data of 7 patients, 4 in the PEG group and 3 in the PEG-S group, had to be excluded from analysis due to an empty battery of the Pillcam while the capsule was still in the small bowel. Therefore, a total of 57 patients were included in this study of which 30 patients in the PEG group (mean age 50 years, 50% men) and 27 in the PEG-S group (mean age 49 years, 52% men). There were no significant differences between the two groups regarding age (p = 0.75) and gender (p = 0.89). Indications for SBCE consisted of anaemia (70.2%), suspected inflammatory bowel disease (IBD) (19.3%), polyps (7.0%) or other (3.5%). Of the 4 patients with polyps as an indication for SBCE, 3 had a known polyposis syndrome and one patient was previously diagnosed with polyps. Patient characteristics are listed in *table 1*.

All patients ingested the capsule without difficulty and no serious adverse events were reported during the examination in the two groups.

Capsule endoscopy imaging quality

The amount of intraluminal gas limiting the visualisation quality of SBCE in the PEG group was significantly higher than in the PEG-S group at 83.3% vs 18.5%, respectively, in the proximal segment (p < 0.01) and 66.7% vs 18.5% in the distal segment (p < 0.01) (*table 2*). No significant difference was seen regarding the amount of faecal contamination limiting visualisation quality between both groups in the proximal segment (80.0% for PEG vs 59.3% for PEG-S, respectively p = 0.2) and distal segment (90.0% for PEG vs 85.2% for PEG-S, p = 0.7, respectively) (*table 3*).

Small bowel transit time and diagnostic yield

The mean small bowel transit time did not differ significantly between the two groups with a mean small bowel transit time of 4.0 hours (SD 1.1) in the PEG group and 3.9 hours (SD 1.3) in the PEG-S group (p = 0.7). A definitive diagnosis was established in 13 patients (43.3%) in the PEG group and 6 patients (22.2%) in the PEG-S group (p = 0.16).

Use of anti-foaming agents in the Netherlands

We assessed the use anti-foaming agents in SBCE bowel preparation of 16 hospitals. Of these 16 hospitals, 3 (18.8%)

Table 1. *Patient characteristics and indications for SBCE in the PEG and PEG-S cohorts*

	PEG (n = 30)	PEG-S (n = 27)	Total (n = 57)
Age (mean, SD) (years)	50.2 (20.2)	48.6 (17.2)	49.4 (18.7)
Gender (male/female)	15/15	14/13	30/27
SBCE indication (n, %)			
- Anaemia	22 (73.3)	18 (66.7)	40 (70.2)
- Suspected IBD	3 (10)	6 (29.6)	11 (19.3)
- Polyps	3 (10)	1 (3.7)	4 (7)

IBD = inflammatory bowel disease; PEG = polyethylene glycol, S = simethicone.

Table 2. *Amount of intraluminal gas in the proximal and distal segment in the PEG group and PEG-S group*

Intraluminal gas	PEG (n = 30)	PEG-S (n = 27)	P-value
Proximal segment			
- Grade 0-1 (n, %)	5 (16.7)	22 (81.5)	
- Grade 2-3 (n, %)	25 (83.3)	5 (18.5)	< 0.01
Distal segment			
- Grade 0-1 (n, %)	10 (33.3)	22 (81.5)	
- Grade 2-3 (n, %)	20 (66.7)	5 (18.5)	< 0.01

See methods section for definitions of grade 0-3. PEG = polyethylene glycol, S = simethicone.

Table 3. *Amount of faecal contamination in the proximal and distal segment in PEG group and PEG-S group*

Faecal contamination	PEG (n = 30)	PEG-S (n = 27)	P-value
Proximal segment			
Grade 0-1 (n, %)	6 (20.0)	11 (40.7)	
Grade 2-3 (n, %)	24 (80.0)	16 (59.3)	0.2
Distal segment			
Grade 0-1 (n, %)	3 (10.0)	4 (14.8)	
Grade 2-3 (n, %)	27 (90.0)	23 (85.2)	0.7

See methods section for definitions of grade 0-3. PEG = polyethylene glycol, S = simethicone.

were academic hospitals, 8 (50%) were regional teaching hospitals and 5 (31.3%) were peripheral hospitals.
Of all contacted hospitals only 3 (18.8%) used an anti-foaming agent prior to SBCE as standard practice. One hospital (6.3%) reported not to use an anti-foaming agent as standard practice, but it was available to use in specific cases. Of the 3 hospitals routinely using anti-foaming agents, 2 were academic hospitals and 1 was a regional teaching hospital. Two of these hospitals were located in the same region in the Netherlands. The other 12 hospitals (75%) reported no use of anti-foaming agents prior to SBCE.

DISCUSSION

This study evaluates the effect of adding simethicone to a bowel preparation regimen with PEG prior to SBCE and showed an improvement in visualisation of small bowel mucosa by significantly reducing the amount of intraluminal gas in both the proximal and distal small bowel. However, the addition of simethicone did not have an effect on the amount of faecal contamination, small bowel transit time and diagnostic yield. The use of anti-foaming agents in SBCE preparation is not standard practice in the Netherlands.
An increase in the quality of small bowel visualisation by adding simethicone to a bowel preparation of PEG compared with fasting is in line with several randomised studies and a systematic review.[13-17,20] Moreover, the preparation regimen of PEG with simethicone proved to improve small bowel visualisation in children.[21] The quality of small bowel visualisation may be influenced by intraluminal gas, debris and juices. In this study, a bowel preparation of PEG and simethicone reduced intraluminal gas and thereby improved visualisation. However, it did not reduce the amount of faecal contamination possibly limiting the quality of visualisation. Similar results were obtained by Rosa et al.[16] who demonstrated that a preparation of PEG and simethicone leads to a reduction of air bubbles in the entire small bowel while not reducing intraluminal fluid and debris. In contrast to our findings, this reduction was observed in comparison with fasting and not when comparing with PEG only. Our study seems to be the only study to show a decrease of intraluminal gas and no effect on faecal contamination when comparing bowel preparation of PEG and simethicone versus PEG only.
A few studies also investigated the effect of simethicone in reducing faecal contamination. Evaluation of faecal contamination is useful when assessing the quality of small bowel visualisation since this is not only influenced by intraluminal gas but also by other factors possibly limiting visualisation of the small bowel mucosa. Our findings are in line with two randomised studies which also demonstrated no effect of simethicone on intraluminal fluid and debris.[12,16] Only one study assessing fluid and debris in the context of small bowel visualisation reported an increase of the quality of visualisation in the distal small bowel when using simethicone and PEG compared with PEG only.[14] That study also showed that PEG only led to a better quality of small bowel visualisation compared with fasting. Importantly, the amount of PEG used in their study was less (1 litre) than in our study (2 litres) while the amount of simethicone was higher (300 mg). This leads to the hypothesis that the increase in the quality of small bowel visualisation reported in their study might be caused by a reduction of intraluminal gas rather than a reduction of intraluminal debris and fluids. Moreover, it is to be expected that adding simethicone to a preparation of PEG does not lead to a decrease of faecal contamination since simethicone only reduces the surface tension of air bubbles.
The present study showed that the addition of simethicone to a bowel preparation with PEG has neither an effect on small bowel transit time nor on diagnostic yield. This finding is supported by most other studies comparing a preparation of PEG and simethicone to PEG except for one study in which the addition of simethicone led to a significantly longer small bowel transit time.[12-14,16,22] To our knowledge, no previous study has reported a better diagnostic yield after adding simethicone to PEG.[12,16,21,22] Although simethicone causes a better visibility of the small bowel mucosa, this does not lead to an increase in positive findings. Hence, simethicone causes a better quality of small bowel visualisation but does not lead to a better diagnostic yield. A possible explanation might be that visualisation is influenced by several other factors than intraluminal gas. Another explanation might be that all these studies are underpowered to detect a significant positive effect on diagnostic yield. Overall, the rate of positive findings in our study is low. This could be explained by the fact that SBCE has become a more widely used diagnostic instrument since its introduction in 2000 with a more flexible indication and therefore may lead to more patients undergoing SBCE without underlying pathology.[23]
This study demonstrated that the use of simethicone prior to SBCE is not standard practice in the Netherlands. Although SBCE guidelines did not reach consensus on the standard preparation regimen, previous literature demonstrated improvement in small bowel visualisation by simethicone. The present study emphasises this improvement in the quality of small bowel visualisation. Moreover, the costs of simethicone are low, there have been no serious adverse events reported when using simethicone prior to SBCE and it is widely available in endoscopy units for foam reduction for oesophagogastro-

duodenoscopy and colonoscopy.[14,15,17] Therefore, we suggest to consider the use of simethicone in bowel preparation prior to SBCE in the Netherlands.

This study has several limits. First, patients were not randomly allocated to either the purgative or purgative with simethicone cohort. On the other hand, the two assessors evaluating the images were blinded to which preparation patients had received. Second, the two groups were relatively small, however big enough to obtain significant results regarding quality of small bowel visualisation. Another limitation is the assessment of intraluminal gas and faecal contamination. This is measured by a relatively subjective scale which has not been validated. The scale we used was also used by Ge et al.[15] Although recent studies have proposed a validated scale, at the time of our study no validated scale was available.[24,25] It is to be questioned if a quantitative measuring method (i.e. the counting of air bubbles) has an additional value for clinical practice. The scale we used seems to be closely related to the evaluation of SBCE images in daily practice.

In conclusion, this study demonstrates that a preparation of PEG and simethicone prior to SBCE improves the visualisation quality of the small bowel by reducing intraluminal gas. Moreover, the use of anti-foaming agents in SBCE preparation is not standard practice in the Netherlands. To date, there is no consensus on a standardised bowel preparation regimen prior to SBCE. Considering the potential benefit, low costs and good safety profile, we recommend simethicone as part of standard bowel preparation in patients undergoing SBCE. As demonstrated by our study and previous literature, the addition of simethicone does not improve diagnostic yield. Therefore, we recommend that future research should focus on stricter purgative regimens in order to investigate its potential beneficial effect on diagnostic yield.

DISCLOSURES

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ORIGINAL ARTICLE

Hurry up, it's quiet in the emergency department

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ABSTRACT

Introduction: Emergency department (ED) crowding is a contemporary problem. Solutions are multiple, but often involve a lengthy implementation process and/or substantial funding. Therefore, it is important that in the meanwhile, we aim to identify simple strategies, focussing on optimising efficiency of the available resources, which can be adopted in the ED here and now.

Methods: We made a careful analysis of inflow, throughput and outflow data of all 24,823 patients visiting the ED of a large teaching hospital in the year 2015, and looked in more detail at the 10 days with the longest average throughput times.

Results: The average throughput time during the study period was 130 minutes. The time between inflow and outflow peaks was well beyond the average daily ED throughput time, indicating that the 'midday surge' in patient arrivals could not be handled adequately by the ED system. For the 10 days with the longest average throughput times, we found a very distinctive pattern, with a backlog of patients building up in the morning hours when maximum bed capacity had not yet been reached. This backlog had consequences during a significant part of the day.

Conclusion: Improved timing of internal efforts in the ED based on careful analysis of ED performance data should be an integral part of a system approach to prevent ED crowding.

KEYWORDS

Crowding, emergency department, throughput time

INTRODUCTION

Crowding is defined as a situation in which the identified need for emergency services outstrips the available resources in the emergency department (ED), hospital, or both,[1] and forms a universal problem for EDs.[2] Various studies have shown that crowding is not only bad for patient satisfaction, it also actually places the patient at risk: complication rates are higher and even mortality is higher.[3-5] ED crowding is a multifactorial problem, spanning the entire healthcare delivery system. Factors contributing to crowding can be categorised as increasing inflow (e.g. inappropriate ED use), decreasing throughput (e.g. inappropriate personnel capacity) or diminishing outflow (e.g. a lack of in-hospital beds).

Crowding is a very contemporary problem in the Netherlands. Van der Linden et al. demonstrated in 2013 that 68% of hospitals experienced crowding several times a week or even daily.[6] Over the last couple of years a sharp increase in the number of ambulance bans declared by hospital administrators as a response to crowding was observed,[7] resulting in longer transport times, which in itself can affect the quality of care provided.

Solutions to crowding are not universal, but can be found in diminishing inflow, shortening throughput times or improving ED outflow. Reducing inflow can be realised by, for example, better identification of patients who can be treated in a non-urgent care setting, by improving collaboration with general practitioners or by a temporary ambulance ban. Shorter ED throughput times can result from minimising the time needed for diagnostic tests or by increasing personnel capacity in the ED, whereas improved ED outflow can be realised by, for instance, creating observation wards.[8] However, there is a major lack of evidence around many of these interventions,[9] and implementation often requires careful mutual adjustment with all parties involved and/or additional funding. This can be a lengthy process when you feel the burden of ED crowding every day. It is important that, in the meanwhile, we aim to identify simple strategies focussing on optimising efficiency of the available resources, which can be adopted in the ED here and now.

Therefore, the objective of the current study was to examine inflow and outflow patterns of an average ED in order to investigate whether it is possible to improve the timing of internal efforts as a potential measure to prevent crowding.

METHODS

Study setting and population

This is a retrospective cohort study of inflow, throughput and outflow data of all patients visiting the ED of the Medical Center Leeuwarden in the year 2015. The Medical Center Leeuwarden is a 671-bed teaching hospital in the northern part of the Netherlands, and is a regional centre for e.g. cardiac interventions and vascular surgery. At the time of our study the ED had 17 beds, and has an annual census of around 25,000 patients/year, which is the average ED size in the Netherlands.[10]

Data acquisition

Performance data were collected retrospectively from the electronic hospital chart used at the time of presentation (Mirador). Data recorded included the arrival number (unique number), patient's triage category (according to Manchester triage system), type of referral (general practitioner, emergency medical services (EMS), self-referral, other), destination after emergency department (discharge/hospitalisation/other), arrival date and time, triage date and time, and discharge date and time.

Data analysis

The average throughput time was calculated for all patients as the difference between inflow and outflow time, and stratified by the time of the day. In order to investigate the relation between inflow, throughput and outflow, a convenience sample of the 10 busiest days (as measured by the longest throughput times) was studied. For each of these days the cumulative number of patients arriving, being triaged and being discharged was analysed as a function of the time of the day. All plots were constructed using Microsoft Excel (Microsoft corp. Seattle, USA).

Ethics

Our study only involved analysis of department performance data and as such was determined to be exempt research by our local ethical committee (protocol number nWMO2017/225).

RESULTS

During the study period, 24,823 patients attended our ED. The majority (79%) of the patients seen in the ED were referred by their general practitioner and/or the EMS service, and 51% of the patients had a triage urgency of 1-2 (highest urgency categories of the 5-point Manchester triage system). Average throughput time for our population was 130 minutes.

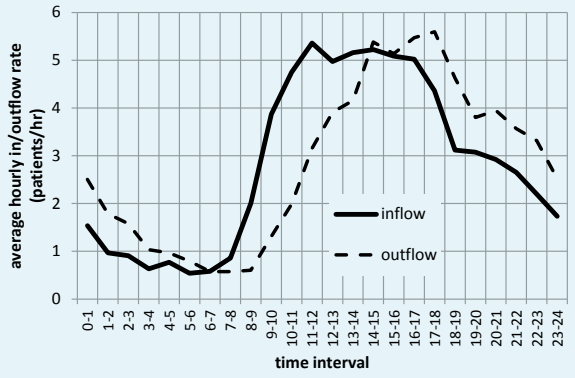
For our study population as a whole, we discovered a characteristic ED input pattern, with relatively quiet hours until the early morning and a sharp increase in the number of patients attending the ED in the course of the morning (*figure 1*). Inflow peaked around 11.00 AM, whereas discharge (outflow) peaked later on the day, around 6.00 PM. The time between inflow and outflow peaks was well beyond the average daily ED throughput time (difference between inflow time and outflow time) of 130 minutes as found for this study period.

In the convenience sample of the 10 days of 2015 with the longest throughput times, we discovered a very distinctive pattern too (*figure 2*, example of one of these days). During the night the cumulative number of patients being discharged tightly follows the number of new patients attending the ED. As a consequence, by 9.00 AM the ED is nearly empty. However, after 9.00 AM more patients start to arrive, and the ED capacity gradually fills up until around 1.00 PM when maximum capacity (17 beds) is reached. Then there is a sudden rise in the number of patients being discharged, and from this moment on, throughput time decreases again, as can be seen from the horizontal distance between the curves in *figure 2*. However, it was not until 4.00 PM before the inflow and outflow were in equilibrium again. Only then did the total number of patients present in the ED start to decrease slightly, and capacity for new patients could be created (*figure 1*).

DISCUSSION

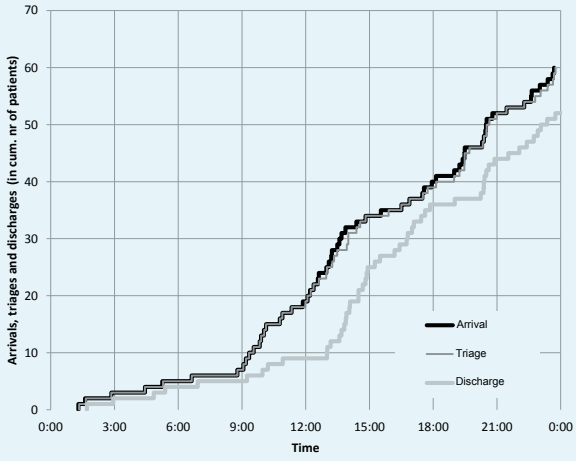
ED crowding is a problem of all times, and countless solutions have been proposed over the last decades to alleviate the burden.[10] These solutions concentrate on ED inflow, throughput and outflow. Of these, uncontrolled inflow is usually perceived as a big contributing problem, which is why many measures have been investigated to reduce inflow. However, inflow factors are hard to control by individual hospitals, since they are highly influenced by demographic, and socioeconomic factors and by the availability and concentration of care.[11] Most Western countries (the Netherlands included) face an ageing population. People are not only getting older, with a resultant increase in comorbidities, they also live longer independently instead of in institutions. When attending the ED, they often have multiple problems. As a result, they have a longer than average length of stay, use more ED resources, and often have to be hospitalised.[7] At the

Figure 1. *Average patient inflow and outflow in the ED as a function of the time of the day*



The vertical axis represents the hourly average number of patients arriving (inflow) or being discharged (outflow) from the ED. The horizontal axis represents the time of the day.

Figure 2. *Patient arrival, triage, and discharge as a function of time of the day on days with a long ED throughput time*



The vertical axis represents the cumulative number of patients arriving, being triaged or leaving the ED. The horizontal axis represents the time of the day. The number of patients being treated at one moment in the ED is represented by the vertical distance between the thick dark line (patient arrival) and the thick grey line (patient discharge). Throughput times are represented by the horizontal distance between the thick dark line (patient arrival) and the thick grey line (patient discharge).

same time, the government policy to concentrate acute care has resulted in a steady decline in the number of 24/7 EDs in the Netherlands over the last five years (from 93 to 87).[12] These factors contribute to an increase in the number of patients presenting to the ED with complex problems. Since individual hospitals are unable to address these factors, they usually tend to focus on measures to reduce the inflow of patients without urgent or complex complaints, such as self-referring patients with sprains, or patients with planned re-visits. However, it has never been demonstrated that these patient categories contribute to crowding.[13]

Therefore, hospital administrators should re-direct their focus to ED throughput, and aim to keep throughput times of all patients presenting to the ED as short as possible. This involves a careful analysis of department performance data in order to determine how much personnel is mandatory, which type of personnel should be contracted (nurses, physician assistants, emergency physicians, or other specialists) and how their shifts should be scheduled. We performed such a throughput analysis for our department and found that inflow peaked around 11.00 AM, whereas outflow peaked around 6.00 PM. Based on the average throughput time of 130 minutes in our study population, the increase in output would have been expected around 1.00 PM. This indicates that the 'midday surge' in patient arrivals could not be handled adequately by the ED system. From the analysis of the 10 days with the longest throughput times, it becomes clear that throughput times are longer in the morning hours, when it is relatively quiet. When the ED is filling up, with the prospect of crowding, around 1.00 PM, throughput times are starting to decrease again. However, the backlog of patients that was building up during the morning hours had consequences during a significant part of the day, since it was not until 4.00 PM before inflow and outflow were in equilibrium again. Despite the fact that only a few beds are being used in the morning, this is the right time to speed up processes to avoid a backlog of patients building up. This may seem counterintuitive, but accepting longer throughput times during the relatively quiet hours results in patient accumulation in the ED later in the day.

Although we have not searched for reasons explaining the slower throughput times in the mornings, we speculate that several factors might contribute to this finding. First, there is a change of shift early in the morning. Patients arriving just before this change and who do not require immediate diagnostic studies or therapeutic interventions are usually handed over to the next shift (and therefore have to wait longer before they are seen by a doctor). Second, personnel capacity is not yet maximal during the early morning hours. Although the absolute number of patients attending the ED during the morning hours is lower than during the afternoon, the number of patients per nurse/doctor can be higher than during the busy hours. Furthermore, the pressure perceived by ED personnel to speed up the process is lower in the morning, since there is still capacity left in the ward to receive new patients. Finally, outflow factors might play a role as well, with less hospital beds being available during the morning hours when admitted patients have not yet been discharged. Therefore, it is important that hospital

administrators schedule sufficient personnel to be able to discharge clinical patients early in the morning and to treat ED patients promptly during the relatively quiet hours. Healthcare providers at the same time should deliver care during these hours with the same efficiency as they aim for during the busy hours.

Our study has several limitations. First, it is a retrospective study, and thereby relies on data completeness and accurateness of registration. Second, our study is solely focused on throughput. A longer average throughput time during the quiet hours is just one of many factors contributing to crowding.[1-4] As stated in our introduction, crowding is a multifactorial problem, and a focus on optimisation of the internal ED processes should not take place without consideration of outflow possibilities at the same time. Finally, even though the average ED throughput time of 130 minutes of our ED is comparable to the Dutch national average,[14] inflow and outflow patterns cannot be generalised across various hospitals, since patient populations and ED staffing vary widely.

However, despite these shortcomings, our findings demonstrate that critical analysis of ED performance data can identify unexpected factors contributing to crowding. Rescheduling of ED personnel based on site-specific inflow and outflow patterns can be accomplished quickly and at relatively limited costs compared with many other measures. Therefore, we recommend that a careful site-specific analysis of inflow and outflow patterns is always made before other, more complex and/or costly, measures are instituted to prevent ED crowding.

CONCLUSION

Improved timing of internal efforts in the ED based on careful analysis of ED performance data should be an integral part of a system approach to prevent ED crowding.

DISCLOSURES

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CASE REPORT

Glucarpidase treatment for methotrexate intoxication: a case report and review of the literature

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ABSTRACT

High-dose methotrexate (MTX) induced acute kidney injury can lead to sustained high systemic MTX levels and severe toxicity. A 39-year-old man with lymphoblastic T-cell lymphoma was admitted to our intensive care unit with elevated serum creatinine and prolonged high serum MTX levels. Standard supportive care was complemented by the addition of a relatively novel agent, glucarpidase, which rapidly lowered the extracellular levels of MTX. Several case series support this effect of glucarpidase, but no randomised controlled trial has been performed to show this leads to better outcome. Furthermore, glucarpidase might negatively affect leucovorin rescue therapy. Lastly, glucarpidase carries a significant financial burden. Based on the current evidence we cannot recommend glucarpidase until further research elucidates its role in the treatment of MTX toxicity. There is no randomised clinical evidence to support its use in severe cases and theoretical evidence suggests that after prolonged exposure to high MTX levels glucarpidase administration is unable to reverse high intracellular MTX. We recommend that new randomised controlled studies be aimed at early administration of glucarpidase in patients with high MTX levels shortly after administration to prevent direct toxic effects of MTX on kidney function and further uptake into cells.

KEYWORDS

Glucarpidase, methotrexate, toxicity

What was known on this topic?

Methotrexate (MTX) toxicity is a rare, but serious complication of high-dose MTX therapy often compounded by reduced clearance due to direct nephrotoxicity. Glucarpidase effectively and rapidly reduces extracellular MTX levels almost completely, but has no effect on intracellular levels.

What does this add?

Despite largely positive observational studies showing fast and significant effects on plasma MTX levels, there are several issues associated with glucarpidase. First, there are no randomised controlled studies that show a beneficial effect on clinical outcome compared with conservative therapy. Secondly, there are serious concerns about the efficacy of leucovorin therapy after glucarpidase administration. And lastly, glucarpidase therapy in recommended dosages carries a significant financial burden. For these reasons glucarpidase is not recommended for the treatment of MTX toxicity until further randomised studies show improved outcome.

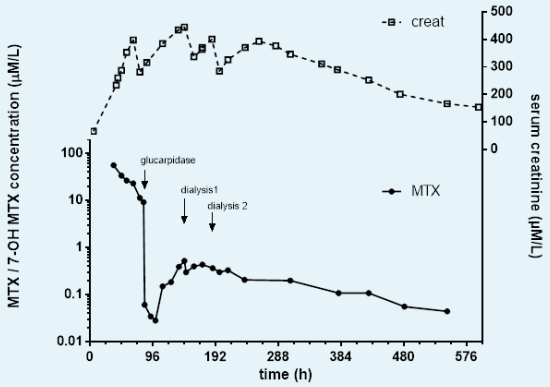
INTRODUCTION

Methotrexate (MTX) is an important chemotherapeutic agent for many oncological indications. MTX disrupts cell repair and proliferation by inhibition of folate reduction through the dihydrofolate reductase enzyme in both malignant and healthy cells. Reduced folates are used as cofactors in DNA and RNA synthesis.[1,2] High-dose MTX therapy, generally defined as > 500-1000 mg/m^2, is therefore followed by administration of leucovorin to counteract the effects of MTX on healthy cells. Leucovorin itself is a reduced folate, bypassing the inhibition of MTX and reducing its cytotoxic effects. High-dose MTX therapy carries the risk of acute kidney injury (AKI) by precipitation of MTX in the renal tubules.[1] Volume depletion and acidic urine are major risk factors for

MTX precipitation. Therefore, hyperhydration and urine alkalinisation are vital parts of MTX treatment protocols. MTX-induced AKI has the potential to induce a vicious circle in which delayed clearance maintains high systemic MTX levels, in turn causing further kidney injury. Sustained high systemic levels of MTX may lead to myelosuppression, hepatic and pulmonary toxicity, neurotoxicity and Stevens-Johnson syndrome. Toxicity plasma concentration thresholds vary based on the organ system, but it has been reported there is a greater risk for toxicity with plasma levels greater than 10 µM at 24 hours. Empirically developed nomograms are often used 24 to 36 hours post infusion to determine if patients are at high risk for MTX toxicity and to pharmacokinetically guide leucovorin rescue therapy based on the MTX serum concentrations and the time post MTX infusion.[1]

Here we describe a case of MTX intoxication in which standard supportive therapy was complemented by glucarpidase, a relatively novel treatment for MTX intoxication. We then review the available evidence to support this treatment.

Figure 1. *MTX serum concentrations and creatinine levels during the course of treatment*



CASE REPORT

A 39-year-old male with a history of Crohn's disease was admitted to our ICU with increased serum creatinine (from 66 to 398 µmol/l) and MTX levels (23 µmol/l) 70 hours after high-dose (5 g/m²) MTX for acute lymphoblastic T-cell lymphoma, despite preventive measures including leucovorin, intravenous hydration and urine alkalisation. Leucovorin therapy was intensified based on treatment protocols as described in the HOVON 100 ALL trial,[3] while vigorous hydration and urine alkalisation were continued.

Because of progressive renal failure under maximum supportive therapy, addition of glucarpidase was considered at admission. Glucarpidase was ordered from Clinigen Healthcare Ltd. in the United Kingdom and was delivered to our hospital the next day. Eighty-five hours after initiation of MTX treatment, serum MTX levels had decreased to 12 µmol/l. Glucarpidase was administered in a single dose of 50 IU/kg and within one hour the serum MTX level had decreased to 0.10 µmol/l (*figure 1*).

In the days after glucarpidase treatment a small, but significant rise in serum MTX levels to a maximum of 0.63 µmol/l was noted. Creatinine levels remained elevated (*figure 1*). In the following days, the patient received two sessions of haemodialysis with a minimal effect on the serum MTX level at a sieving coefficient of 0.08.

The patient was discharged to the general ward. His renal function improved in the following weeks and after one month his estimated glomerular filtration rate (eGFR) had normalised to pre-toxicity levels. Four months later a PET-CT scan showed complete remission.

DISCUSSION

MTX intoxication is a life-threatening complication of high-dose MTX. Its incidence has decreased after the introduction of MTX treatment protocols that include screening for third space fluid collections such as ascites and pleural fluid, intensive hydration and alkalinisation, and leucovorin therapy. Once this complication occurs, however, it still carries a high risk for severe morbidity and mortality. The goal is to treat the effects that have already occurred and to minimise further toxicity. Our patient received glucarpidase in addition to intensified leucovorin rescue treatment, hyperhydration and urine alkalisation, and recovered.

Extracorporeal techniques such as haemofiltration and haemodialysis have been used to enhance MTX clearance. Evidence for the efficacy of these techniques is mostly limited to case reports with varying efficacy.[4-13] High-flux haemodialysis is thought to be most effective in removing MTX. With all extracorporeal techniques a significant rebound effect necessitating multiple treatments often occurs.[14] The risks of these techniques are haemodynamic instability and introduction of invasive catheters in patients prone to infection and bleeding diathesis.

Recently, glucarpidase has come under attention as an alternative to extracorporeal techniques. Glucarpidase, or Voraxaze™, is a carboxypeptidase that can eliminate extracellular MTX by hydrolysing its terminal carboxyl-glutamate residue, producing inactive metabolites such as 4-deoxy-4-amino-N[10]-methylpteroic acid (DAMPA).[15] Four

case series reported an important reduction in extracellular MTX levels in adult patients after a single dose of glucarpidase.[16-19] Widemann et al. performed a pooled analysis of efficacy data from these four multicentre, single arm, compassionate use clinical trials using protocols from 1993-2007.[20] This analysis showed that glucarpidase can rapidly and safely reduce extracellular MTX levels by a median of 99% and a clinically important reduction in 59% of patients. Side effects of glucarpidase treatment, while difficult to distinguish in patients with symptoms of MTX toxicity, were rare and self-limiting in all of the case series. Paraesthesia and flushing were most often reported.

The effects of glucarpidase on intracellular concentrations of MTX are less clear. It is known that with sufficiently high MTX concentrations over time MTX is polyglutamated intracellularly.[21,22] The polyglutamation process prohibits these MTX molecules from leaving the cell and increases their affinity for the target enzymes involved in reducing folates. MTX toxicity therefore is concentration and time dependent. The rate and extent at which glucarpidase reduces extracellular MTX levels compared with extracorporeal techniques preventing further polyglutamation might be its main advantage. Also, by reducing systemic MTX levels further precipitation in the renal tubules might be prevented. Glucarpidase, however, does not directly affect the intracellular concentration of MTX.

Because MTX and leucovorin compete for a common uptake path into the cell, proportionally higher concentrations of leucovorin are required to achieve rescue in the presence of MTX.[1] Plasma MTX concentrations should always be monitored closely and leucovorin therapy intensified and continued until MTX serum levels have decreased to non-toxic levels and there are no signs of ongoing toxicity. Reducing extracellular MTX levels might enhance leucovorin uptake into the cell. However, leucovorin also competes with MTX as a substrate for glucarpidase, although with a lower affinity. This effect decreases the exposure to leucovorin for up to 26 hours after administration of glucarpidase. A reduction of the efficacy of leucovorin therapy by glucarpidase poses a serious risk. This concern was raised in the withdrawal report for glucarpidase at the European Medicines Agency (EMA).[23]

Given the lack of evidence of the effect of glucarpidase on intracellular levels of MTX and the possible negative effect it has on leucovorin rescue therapy, it is unfortunate that none of the case series compared the results of glucarpidase treatment to patients receiving standard supportive care in clinically relevant outcome parameters such as mortality or time to return to normal kidney function. In fact, despite glucarpidase treatment, mortality in one case series was as high as 23%.[18] In our patient renal function returned to near baseline levels more than one month after glucarpidase therapy.

Glucarpidase is currently not registered on the European market and only available directly from the manufacturer. Orders are generally delivered within 24 hours within the Netherlands, but this still causes a delay in initiation of treatment.

At the time of application to the EMA, no dose-finding study had been performed to determine optimal dosage. A dose of 50 U/kg is recommended by the manufacturer; however, the proposed dose is not justified by clinical data and it is not shown that repeated use of glucarpidase is beneficial. Animal studies suggest that lower doses might have the same results.[23] In two of the case series some patients received lower doses of glucarpidase. Unfortunately, the decrease in MTX levels was not reported separately for these patients.[17,18] In a normal adult of 70 kg, treatment with 3500 units can cost up to 60,000 euro. A lower recommended dose could help to reduce the cost of treatment considerably.

CONCLUSION

MTX toxicity is a rare, but serious complication of high-dose MTX therapy. Supportive measures include first and foremost intensified leucovorin therapy together with hydration and urine alkalisation to maximise renal clearance. Glucarpidase is a relatively new agent that can rapidly and safely reduce extracellular MTX to non-toxic levels. However, glucarpidase does not reduce intracellular MTX levels and might reduce efficacy of leucovorin therapy. To date there is no randomised controlled trial comparing it with standard supportive measures on clinically relevant outcome parameters and treatment with glucarpidase carries a significant financial burden.

Because of these issues, we cannot recommend the use of glucarpidase in the treatment of MTX toxicity. There are no randomised clinical data to support the use in severe cases and theoretical evidence suggests that glucarpidase administration is unable to reverse high intracellular MTX concentrations after prolonged exposure to high MTX levels. Glucarpidase might be able to prevent irreversible MTX uptake into cells and limit direct effects of high MTX levels on kidney function. New randomised controlled studies should therefore be aimed at early administration of glucarpidase in patients with high levels shortly after administration of MTX. A recent meta-analysis of the observational data showed that administration of glucarpidase within 96 hours of MTX dosage reduced the development of severe toxicity.[20] New studies should also include different treatment regimens for glucarpidase, since earlier studies suggest that a much lower dosage might be just as effective

and could possibly reduce any deleterious side effects and cost of treatment.

DISCLOSURES

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

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CASE REPORT

Fulminant presentation of oral mucosal leishmaniasis as severe stomatitis and periodontitis

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ABSTRACT

This case report shows an atypical presentation of mucosal leishmaniasis infantum in the oral cavity resulting in severe stomatitis and periodontitis. The patient was immunocompromised because of rheumatoid arthritis for which he used prednisone and methotrexate. He was treated with intravenous liposomal amphotericin B and recovered within four weeks.

KEYWORDS

Leishmaniasis, mucosal, oral, periodontitis, stomatitis, *Leishmania infantum*

What was known on this topic?
Leishmaniasis is an endemic disease in many countries and appears in three main forms: Visceral leishmaniasis, cutaneous leishmaniasis and mucocutaneous leishmaniasis. Exclusive involvement of the mucosa is unusual, especially when it presents as severe stomatitis and periodontitis.

What does this add?
This fulminant case demonstrates a rare, disabling and disfiguring but treatable isolated oral manifestation of mucosal leishmaniasis in an immunocompromised patient, highlighting the importance of a good pathological/microbiological work-up in patients with stomatitis and periodontitis under immunosuppressive therapy.

INTRODUCTION

Mucosal leishmaniasis (ML) is a chronic infection that affects the upper respiratory tract or oral mucosa and is caused by the protozoan parasites of the genus *Leishmania*. Leishmaniasis is found worldwide and is considered to be endemic in approximately 90 countries. It has an estimated prevalence of 12 million infected individuals worldwide, with a global incidence of 1.5-2 million new cases per year. Leishmaniasis is responsible for approximately 80,000 deaths yearly.[1] There are three main clinical forms of leishmaniasis: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and ML. Exclusive involvement of the mucosa is not a novelty,[2] but a fulminant course, as described here, with severe stomatitis and periodontitis, is noteworthy in our opinion.

CASE REPORT

The dentist referred a 40-year-old male because of severe stomatitis (*figure 1*). Inflammatory symptoms had been present for several months, in the absence of fever. His medical history included rheumatoid arthritis for which he used prednisone and methotrexate. The patient originated from Morocco, which he had visited seven months prior to his initial presentation and on several occasions earlier, but he had been living continuously in the Netherlands for most of his life. On physical examination, no signs of abdominal pain were present, and abdominal ultrasound yielded no hepatosplenomegaly.

Except for CRP (10 mg/l) and a leucocytosis (13.9 x 10^9/l) with neutrophilia (11.0 x 10^9//l), full blood count and biochemistry were inconspicuous. HIV, hepatitis B/C, Epstein-Barr virus and cytomegalovirus serology were negative.

We considered a diagnosis of severe periodontitis and stomatitis combined with superficial candidiasis. Anti-fungal therapy was prescribed in combination with oral hygienist treatment, but due to the lack of clinical improvement, eventually all his maxillary teeth had to be removed. On day 7, there were no signs of early healing; instead, the clinical manifestation had worsened. A palatal biopsy was taken, which was indicative of leishmaniasis in view of a deep penetrating ulcerative process. The inflammatory infiltrate consisted mainly of lymphocytes and histiocytes and showed focal small granulomas; numerous histiocytes contained large numbers of intracytoplasmic bodies suggestive of *Leishmania* spp. amastigotes (*figure 2*). Parasitological diagnosis by microscopy of a direct smear of a biopsy showed numerous *Leishmania* parasites, and mini-exon repeat PCR according to Marfurt et al. was positive.[3] Culture was negative, while serological testing by RK39 and DAT tests proved positive. Sequence analysis of the mini-exon repeat PCR product indicated that the parasites belonged to the *L. donovani* complex. Therefore, a PCR and sequence analysis for the *cpb* gene was performed, according to Hide et al., showing *Leishmania infantum* to be the causative species.[4]

The patient was admitted and treated with intravenous liposomal amphotericin B (3 mg/kg every 24 hours for 10 days). Methotrexate was temporarily stopped. Within 14 days, the palate showed significant improvement and returned to normal within four weeks. A biopsy after three months showed no presence of *Leishmania* spp. amastigotes; the PCR was also negative. Without his former therapy, his rheumatoid arthritis exacerbated. Therefore, methotrexate was re-introduced after the PCR from the last biopsy was negative. The patient was rehabilitated with a full dental prosthesis, and he has been followed up for two years with no signs of recurrence.

Figure 1. *The mucosa of the maxilla showing severe inflammation and ulceration*

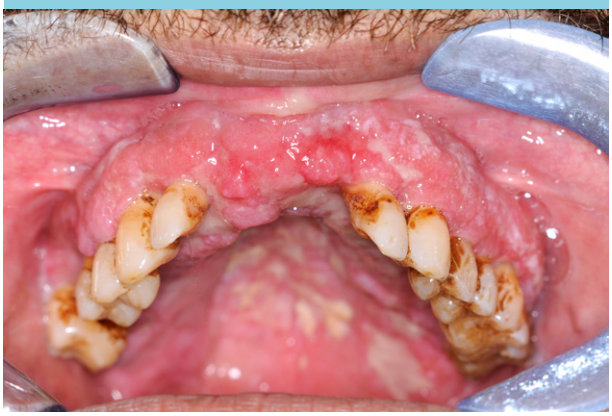
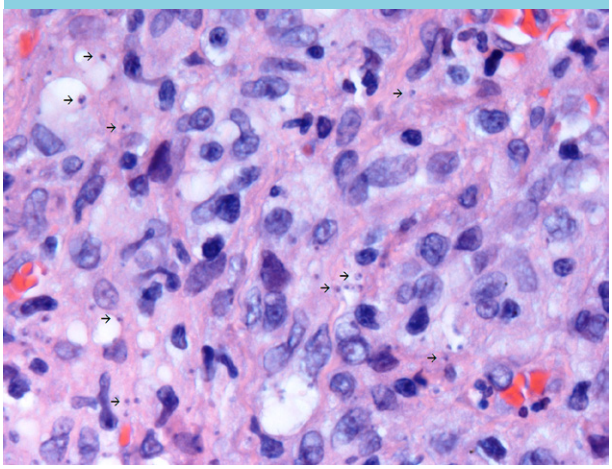


Figure 2. *Detail of palatal inflammatory infiltrate showing large numbers of Leishmania bodies (arrows), mostly located in histiocytes. Haemotoxylin & eosin stain, x630*



DISCUSSION

This case highlights the diagnostic difficulties in patients with exclusively mucosal lesions at an atypical location. Based upon the clinical manifestation, this patient is to be considered as having suffered from ML. It is most often caused by parasites of the *Viannia* subgenus and is considered to be a haematogenous or lymphatic dissemination of amastigotes from a CL lesion to the naso-oropharyngeal mucosa.[5] However, the patient described above did not have a previous or concomitant episode of cutaneous leishmaniasis. ML is mostly caused by reactivation of the disease months or even years after onset of a primary CL, although in some cases there is no history of a cutaneous lesion. Less than 5% of patients suffering from the cutaneous form will develop mucosal metastatic disease.[2] In the Old World, ML can be diagnosed as a sole entity or concomitantly with VL. *L. infantum* is known for causing VL and spreads through the mononuclear phagocyte system. This patient did not have any fever or other symptoms of VL suggestive of visceralisation. Furthermore, bacterial (super)infection occurs frequently in VL under immunosuppressive therapy,[6] which could explain the severe periodontitis and stomatitis of the maxilla in this case. The absence of other clinical symptoms is exceptional. In this patient an Old World species, *L. infantum*, is causing solitary ML, which is unusual. The mucosal manifestation due

to Old World species is not often described in patients with *L. infantum*.[7,8] At present, liposomal amphotericin B appears to be the preferred choice of treatment, because of its short treating period and less adverse effects in comparison with, for example, stibogluconate (Pentostam).[2,9]

Because of the multicultural population in the Netherlands, an increasing incidence is reported, with an estimated 20-30 patients being diagnosed with CL and 5-10 patients with VL every year.[10,11] Furthermore, a solitary ML is extremely rarely encountered in Western Europe. In southern Europe leishmaniasis is suggested to be a latent public health threat, because of a high prevalence of asymptomatic human carriers of *L. infantum*.[12] This is demonstrated by the increase of co-infections with human immunodeficiency virus and leishmaniasis, with leishmaniasis becoming the third most frequent opportunistic parasitic disease after toxoplasmosis and cryptosporidiosis.[8,13] In order to facilitate a favourable patient outcome, it is important to consider isolated ML if the history of possible exposure warrants to include this rare condition in the differential diagnosis.

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PHOTO QUIZ

Pancytopenia in a young girl with skin lesions

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CASE REPORT

A 14-year-old-girl presented with complaints of being easily fatigued and bleeding gums of two weeks' duration. She had a history of seizures in childhood. Physical examination demonstrated papular lesions on the nose, and cheeks consistent with facial angiofibromas (*figure 1*) There were ash-leaf hypomelanotic macules on the limbs (*figure 2*). No oral or periungual fibromas were seen. Examination of the cardiovascular and respiratory system was unremarkable. Her blood investigations revealed a haemoglobin of 4.59 mmol/l, elevated leucocyte count 4.93 x 10^9/l with 78% abnormal cells and thrombocytopenia 1.6 x 10^9/l. Bone marrow showed immature cells having irregular nuclei with folding and invagination (*figure 3*). The immature cells were peroxidase positive. Magnetic resonance imaging of the brain revealed subependymal nodules in the lateral ventricle (*figure 4*).

WHAT IS THE HAEMATOLOGICAL CONDITION CAUSING PANCYTOPENIA AND WHAT IS THE SYNDROME IN THIS PATIENT?

See page 44 for the answer to this photo quiz.

Figure 1. *Papular lesions on the nose, and cheeks consistent with facial angiofibromas*

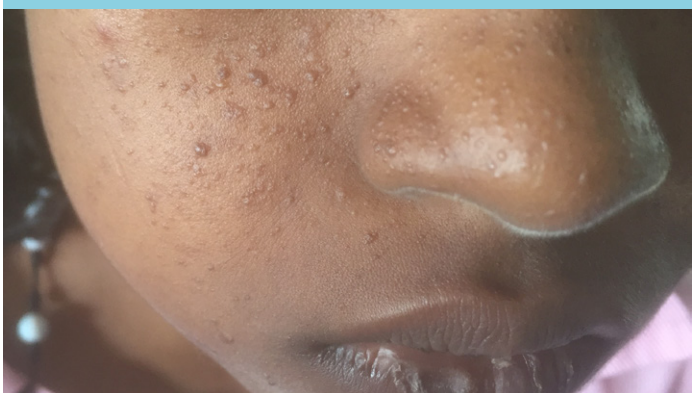


Figure 2. *Ash-leaf hypomelanotic macules on limbs*

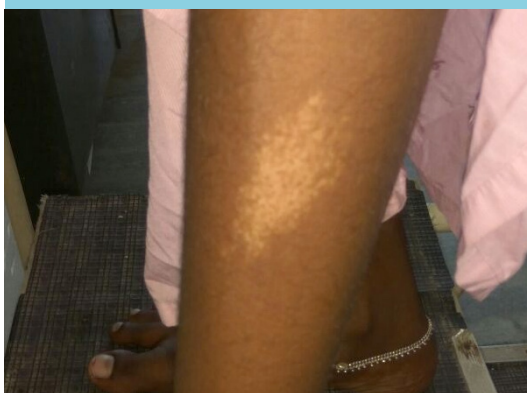


Figure 3. *Bone marrow showed immature cells having irregular nuclei with folding and invagination*

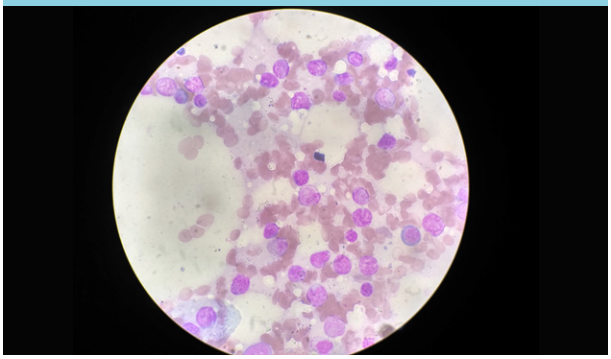
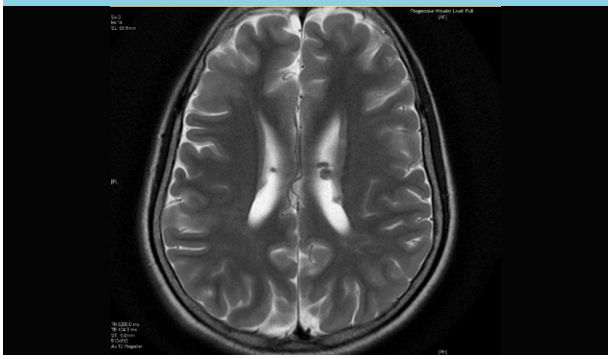


Figure 4. *Magnetic resonance imaging of the brain demonstrated subependymal nodules in the lateral ventricle*



ANSWER TO PHOTO QUIZ (PAGE 43)

PANCYTOPENIA IN A YOUNG GIRL WITH SKIN LESIONS

DIAGNOSIS

The haematological condition is acute myeloid leukaemia and the syndrome in this patient is tuberous sclerosis. Tuberous sclerosis is an inherited neurocutaneous syndrome characterised by multiple benign hamartomas involving brain, eyes, heart, lung, liver, kidney, and skin.[1] It has an autosomal dominant pattern of inheritance with an approximate incidence of 1 in 5000 to 10,000 live births.[2] Tuberous sclerosis can be diagnosed clinically using the criteria from the International Tuberous Sclerosis Complex Consensus Conference.[3] Patients with tuberous sclerosis are at an increased risk of developing malignant tumours involving kidneys, brain, and soft tissues.[4] The risk of malignancy in tuberous sclerosis is approximately 18-fold higher than in the normal population. Downregulation of tuberous sclerosis complex 2 expression has been demonstrated in acute myeloid leukaemia.[5]

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PHOTO QUIZ

From dentist to internist

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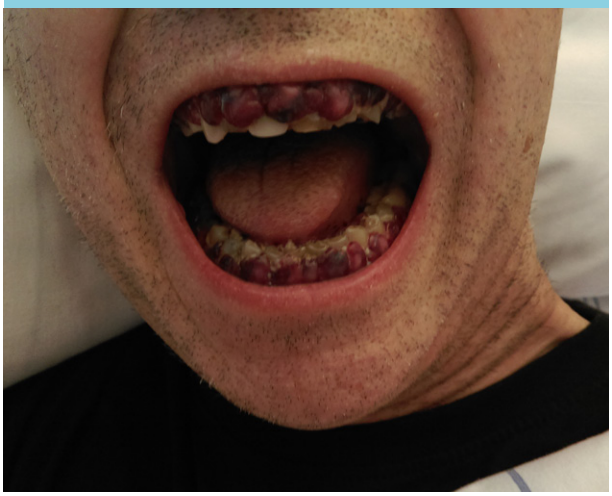
CASE REPORT

A 64-year-old man was referred by his dentist because of remarkably enlarged and vulnerable gums. His chief complaints were nausea, weight loss and haematemesis because of gum bleeding for the last 5 weeks. He has a past medical history of retroperitoneal fibrosis, hypothyroidism and a myelodysplastic syndrome type refractory cytopenia with multi-lineage dysplasia since 2013 for which he received no treatment. His only medication was levothyroxine 75 µg once daily. He does not smoke. Physical examination revealed a fever, marked gingival enlargement (*figure 1*), a 2 cm submandibular lymph node on his left side and several haematomas on both legs.

Figure 1. *Marked gingival enlargement*



WHAT IS YOUR DIAGNOSIS?

See page 46 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 45)
FROM DENTIST TO INTERNIST

DIAGNOSIS

The complete blood count showed a haemoglobin of 4.8 mmol/l, thrombocytes of 11 mmol/l and leucocytes of 8.2 mmol/l. The peripheral blood smear revealed 80% leukaemic blasts, tear drop cells and fragmentocytes. Clotting times and fibrinogen levels were normal. A transformation of his myelodysplastic syndrome into an acute myeloid leukaemia was suspected. This was confirmed by bone marrow which showed 71% blasts with strong positive myeloperoxidase staining and immunophenotyping revealing predominantly myelocytic blasts fitting an acute myeloblastic leukaemia. Tumour cytogenetic and molecular analysis showed a normal male karyotype and no mutations.

Gingival enlargement can be a sign or even a presenting symptom of acute leukaemia, especially when there is a prominent monocytic component.[1] It is not unusual that a dentist is the one who refers the patient to an internist for further analysis. An observational study showed that up to 66.7% of patients with acute monocytic leukaemia have gingival infiltrates or hyperplasia. Followed by 18.5% in patients with acute myelomonocytic and 3.7% with myeloblastic leukemia.[2] For unknown reasons it seems that acute lymphocytic leukaemia rarely causes gingival enlargement.[3] Hyperplasia can be due to direct infiltration of leukaemic cells. In that case it is called a myeloid sarcoma or chloroma. Sometimes, however, cytology only shows a reactive pattern without infiltration.[4] A histological biopsy was not performed in our patient. There is probably a tooth-associated factor in the pathogenesis since leukaemic gum invasion is not seen in people who are edentulous.[2]

Gingival hyperplasia is also a fairly well-known side effect of certain drugs. It has been well described with calcium antagonists, cyclosporine and antiepileptic drugs.[5] More recently also vemurafenib has been identified.[6] Furthermore it can be a manifestation of an autoimmune disease, namely granulomatosis with polyangiitis, Crohn's disease, tuberculosis and sarcoidosis.[7] The obvious therapy is treating the underlying disease or abstaining from the responsible drug.

The patient participated in the European Organisation for Research and Treatment of Cancer (ORTC) 1301 trial and was initially only treated with two cycles of decitabine. Because there was progression of disease under this regimen he was switched to an intensive therapy according to the Hemato-Oncology Adult Netherlands (HOVON) 103 trial. After two cycles of cytarabine, remission was achieved and he was referred to an academic hospital for an allogenic bone marrow transplantation which was successful. With this, his gingival enlargement also improved back to normal.

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PHOTO QUIZ

Fever, abdominal erythema and subcutaneous emphysema

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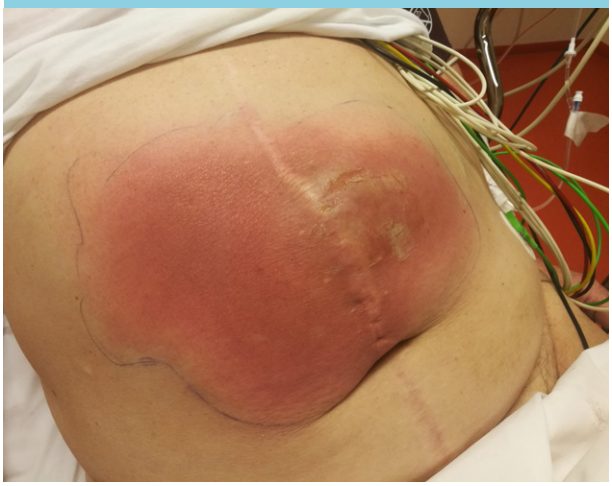
CASE REPORT

A 72-year-old male presented with fever and abdominal erythema (*figure 1*). His medical history included an aortic graft stent (open procedure) in 2009 because of an abdominal aortic aneurysm and a myocardial infarction in 2006. Four days earlier the general practitioner started amoxicillin/clavulanic acid because of a fever, abdominal erythema and suspicion of erysipelas. At presentation signs of septic shock including high fever, high inflammation parameters and hypotension not responding to fluid resuscitation were present but he only experienced mild abdominal pain. During palpation of the abdominal erythema an underlying infiltrate was discovered and crepitus was found, suggesting the presence of subcutaneous emphysema.

Figure 1. *Abdominal erythema*



WHAT IS YOUR DIAGNOSIS?

See page 48 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 47)

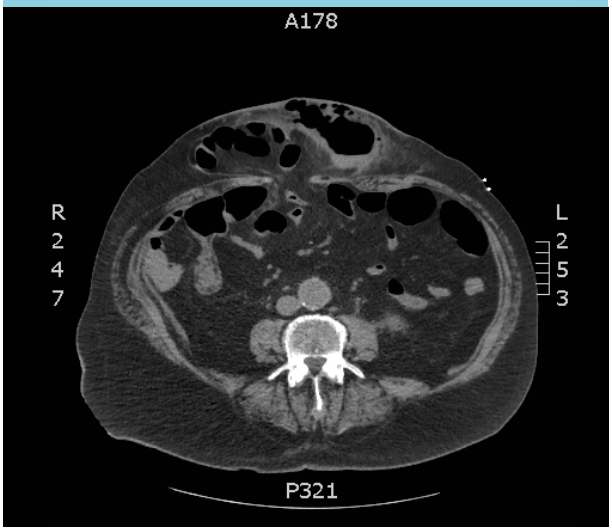
FEVER, ABDOMINAL ERYTHEMA AND SUBCUTANEOUS EMPHYSEMA

DIAGNOSIS

Erysipelas was considered a possible diagnosis by the general practitioner. However, there were signs that make this diagnosis less likely. Although erysipelas can develop in any area of the skin, it is typically found on the lower extremities. One study showed that 77% (48 out of 62 patients) of erysipelas cases involved the lower extremities, 13% involved the upper extremities and in only 3% of cases the lower abdomen was affected.[1] There was no sign of a portal of entry, which is found in most cases,[2] and the patient developed sepsis-induced hypotension after four days of adequate antibiotic treatment. These findings led us to reconsider the diagnosis.

On physical examination an infiltrate was palpable underlying the erythema, and during palpation crepitus was observed that suggested subcutaneous emphysema. Bowel sounds were hyperactive, but the patient did not vomit or experience nausea. A few days later a more detailed medical history was taken and revealed the patient had vomited in the days before presentation. An ultrasound confirmed presence of a fluid collection localised under the possible infiltrate, but was otherwise inconclusive. The surgical department was consulted because necrotising fasciitis was the diagnosis to be ruled out. The erythema, fever, subcutaneous emphysema and septic shock could all be signs of necrotising fasciitis, but the absence of 'disproportionate pain' was atypical.[3] The CT scan of the abdomen showed an incarcerated herniation of the intestine (*figure 2*). The presence of (free) air suggested intestinal perforation. The patient was immediately transferred to the operating room where two perforations of the transverse colon inside of the hernia sac were found. Ten centimetres/four inches of the transverse colon were resected. Contents of the large intestine were only found inside the hernia sac and in the subcutis. The antibiotic treatment given on the ICU consisted of piperacillin/tazobactam as well as fluconazole, which was later switched to anidulafungin because of a positive ascites culture for *Candida albicans*. The ascites culture also showed *Enterobacter cloacae*, *Morganella morganii*, *E. coli* and *Klebsiella pneumoniae*. Of these bacteria only *Morganella morganii* was found in the blood cultures collected at presentation. Because of the condition of the patient, primary anastomosis was postponed and performed during a second procedure three days later. Eleven days after initial presentation the patient could leave the ICU.

Figure 2. *Abdominal CT in axial view showing herniation of the intestine with presence of free air suggesting perforation*



An incisional hernia is the most probable cause of the herniation and incarceration that developed in this patient. It is estimated that 10-15% of patients undergoing a laparotomy incision eventually develop incisional herniation, 60% of these patients are asymptomatic.[4] Research suggests perioperative factors play a role in the development of incisional hernias, for example wound infection and the suture technique.[5] Incisional hernia repairs are performed in 6 to 15% of cases because of strangulation or obstruction.[6] Risk factors for strangulation are a narrow diameter of the hernia sac neck and increasing intraabdominal pressure caused by other abdominal pathology, including intraabdominal sepsis.[7] Treatment of an incarcerated hernia consists of immediate surgical intervention, using the open approach when there is the suspicion of strangulation and the need of bowel resection.[8] Subcutaneous emphysema, or crepitus on palpation, which is associated with necrotising fasciitis, is actually a late sign of this disease (developing during the third and last stage) along with skin necrosis with discoloration and skin anaesthesia.[9] In this case it turned out to be a sign of 'free' air due to perforation.

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