Outcome of treated and untreated asymptomatic bacteriuria in renal transplant recipients

Emmanuelle Boffi El Amari¹, Karin Hadaya²,³, Leo Bühler³, Thierry Berney³, Peter Rohner⁴, Pierre-Yves Martin², Gilles Mentha³ and Christian van Delden¹,³

¹Service of Infectious Diseases, Department of Medical Specialities, University Hospital Geneva, Geneva, Switzerland, ²Service of Nephrology, Department of Medical Specialities, University Hospital Geneva, Geneva, Switzerland, ³Service of Transplantation, Department of Surgery, University Hospital Geneva, Geneva, Switzerland and ⁴Central Laboratory of Bacteriology, Department of Laboratories, University Hospital Geneva, Geneva, Switzerland

Correspondence and offprint requests to: Christian van Delden; E-mail: Christian.vandelden@hcuge.ch

Abstract

Background. No guidelines exist concerning treatment of asymptomatic bacteriuria in renal transplant recipients (RTR). Because of scarce clinical symptoms and fear of complications, such episodes are frequently treated based on subjective criteria without clear clinical benefit, with the risk of selecting resistant pathogens.

Methods. We retrospectively analysed the outcome of 334 asymptomatic Escherichia coli (E. coli) and Enterococcus faecalis (E. faecalis) bacteriuria that occurred in 77 RTR later than 1 month post-transplantation. We distinguished: Type I, high-grade bacteriuria with pyuria; Type II, high-grade bacteriuria without pyuria; Type III, low-grade bacteriuria with pyuria and Type IV, low-grade bacteriuria without pyuria.

Results. None of the 334 episodes was followed by acute rejection or chronic pyelonephritis. One hundred and one (30%) episodes were treated [32 (62%) Type I, 38 (45%) Type II, 13 (36%) Type III and 18 (11%) Type IV]. Evolution to symptomatic urinary tract infection (UTI) was similar between treated and untreated episodes (0/101 versus 4/233, P = 0.32). The four UTI resolved favourably without further complication upon treatment. Persistent asymptomatic bacteriuria occurred in 45 (46%) treated episodes (2 Type I, 27 Type II, 8 Type III and 9 Type IV), with selection of resistant pathogen in 35 cases (78%). Spontaneous bacterial clearance occurred in 138 (59%) untreated episodes (15 Type I, 23 Type II, 9 Type III and 91 Type IV). Negative control cultures tended to be more frequent in treated Type I (P = 0.09) and in untreated Type II episodes (P = 0.08).

Conclusion. Restricting antibiotic treatments for asymptomatic low-grade bacteriuria and high-grade bacteriuria in the absence of pyuria, occurring later than 1 month post-transplantation, might be safe in RTR.

Keywords: antibiotic treatment; bacteriuria; transplantation; urinary tract infection

Introduction

Despite the common use of prophylactic trimethoprim–sulphamethoxazole (TMP–SMX) during the first 6 months post-transplantation, infections of the urinary tract (UTI) remain the most common form of bacterial infection in renal transplant recipients (RTR) [1]. Retrospective studies have suggested that the frequency of UTI in RTR is higher than in the general population, especially during the first month posttransplantation [2, 3]. The incidence ranges from 4 to 74% in this population [1–5]. UTI after renal transplantation have been associated with graft loss, chronic rejection, papillary necrosis and an increased mortality [1, 2]. Specific risk factors include advanced age, female gender, reflux kidney disease prior to transplantation, use of azathioprine and deceased donor [1, 2]. Escherichia coli (E. coli) and Enterococcus spp. are the most frequently isolated bacterial pathogens accounting for >50% of UTI in this population [1, 2, 6, 7]. For E. coli, a unique pattern of uropathogenic serotypes and adherence factors have been recently suggested to contribute to allograft injury in RTR [8]. In non-RTR, clinicians distinguish between upper-UTI (pyelonephritis), lower-UTI (cystitis) and colonization of the lower urinary tract (asymptomatic bacteriuria) [9]. These distinctions are made on the bases of clinical symptoms, quantitative urine cultures and urine sediment analysis. In the absence of symptoms, positive urinary cultures generally do not require treatment [10–12]. However, in RTR, such distinctions are generally not made because of the fear of scarce clinical symptoms and more rapid serious complications [1, 13]. In the absence of clear prospective data, precise treatment guidelines do not exist for this frequent situation [1]. The latest guidelines issued by the ‘Infectious Diseases Society of America’ state ‘No recommendations can be made for screening, or treatment of asymptomatic bacteriuria in
renal transplant recipients (C-III) [12]. As a consequence, treatment strategies for asymptomatic bacteriuria have been more liberal and indiscriminate in RTR, and physicians tend to treat such episodes according to their personal discretion. Lengths of treatments vary considerably, and many episodes of asymptomatic bacteriuria (potentially colonizations) are treated, leading to repeated exposure of RTR to antimicrobial agents. The only objective criteria available to the clinician during an episode of asymptomatic bacteriuria are the level of bacteriuria and of pyuria. We wondered whether the degree of these two criteria influences the outcome of both treated and untreated asymptomatic bacteriuria. We therefore conducted a retrospective study to determine the outcome of both treated and untreated E. coli and E. faecalis asymptomatic bacteriuria that occurred later than 1 month post-transplantation, classified in four distinct groups based on culture and urinary sediment.

Materials and methods

Patients

This retrospective study was conducted on 196 consecutive patients who received a renal allograft at the University Hospital in Geneva, Switzerland from January 1999 to October 2004. Using the database of the Central Bacteriology Laboratory and the clinical records of the University Hospital, we identified 334 distinct episodes of asymptomatic E. faecalis or E. coli bacteriuria, which occurred at least 1 month post-transplantation in 65 kidney recipients and 12 kidney–pancreas or kidney–islets recipients during this period. Fifty-eight per cent were female and the mean age at transplantation was 49 years (range 21–73). Eighty-three per cent had a kidney from a deceased donor (Table 1). The bile drainage of all pancreas recipients was enteric. Causes of end-stage renal diseases are listed in Table 1.

Immunosuppressive therapy

Several protocols were used during the study for induction and maintenance immunosuppression. For induction therapy, 60 kidney recipients received the monoclonal anti-IL2 receptor antagonist basiliximab and 5 received rabbit anti-thymocyte globulin (ATG). Corticosteroids were given in combination with MMF and tacrolimus/cyclosporine. Corticosteroids were progressively decreased from initially 1 mg/kg/day to 5 mg/day at 3 months post-transplantation. Induction therapy for kidney–pancreas recipients consisted of ATG in combination with corticosteroids and for kidney–islets recipients of daclizumab. Maintenance therapy for kidney–pancreas recipients was based on a combination of tacrolimus with MMF or sirolimus, with progressive discontinuation of corticosteroids over 6 months, and for kidney–islets recipients on a combination of tacrolimus and sirolimus. At the time of asymptomatic bacteriuria, corticosteroids were given in combination with MMF and tacrolimus/cyclosporine to 68 patients (Table 1). Six patients were receiving a combination therapy of tacrolimus and MMF and three patients a combination therapy of tacrolimus and sirolimus.

Table 1. Characteristics of 77 patients with asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Age (mean and range)</th>
<th>50 (11–73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>45 (58%)</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>65</td>
</tr>
<tr>
<td>Kidney–pancreas or kidney–islets transplant</td>
<td>12</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>64 (83%)</td>
</tr>
<tr>
<td>Immunosuppressive treatment at the time of bacteriuria</td>
<td>68</td>
</tr>
<tr>
<td>Steroids + MMF + tacrolimus/cyclosporine</td>
<td>6</td>
</tr>
<tr>
<td>Tacrolimus + MMF</td>
<td>3</td>
</tr>
<tr>
<td>Tacrolimus + sirolimus</td>
<td></td>
</tr>
<tr>
<td>Cause of end-stage renal disease</td>
<td>10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>6</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>7</td>
</tr>
<tr>
<td>Polycystic kidney</td>
<td>21</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>10</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>8</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
</tr>
<tr>
<td>Mortality</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Renal graft loss</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

Antibiotic prophylaxis

All patients received a peripherio antibiotic prophylaxis consisting in three doses of 1.2 g amoxicillin–clavulinate, given at 8 h intervals, the first administered 1 h prior to incision. Post-operative prophylaxis consisted of TMP–SMX 480 mg/day for 6 months. Valgancyclovir for cytomegalovirus (CMV) prophylaxis was given to all high-risk recipients (D+/R–) and to all patients receiving ATG for induction therapy. Intermediate risk patients (D+/R+ and D–/R+) were screened weekly with an ultrasensitive polymerase chain reaction and treated pre-emptively with valgancyclovir in the case of positive CMV viraemia.

Parameters studied

We reviewed the medical records for information on demographic characteristics, date of transplantation and positive cultures, concomitant bacteremias, urine analysis and clinical presentation both at the time of positive cultures and the follow-up visit, type of immunosuppression at the time of the positive cultures, type and length of treatment, acute rejection within 1 month of bacteriuria, death and renal graft loss during the study period. Patients with clinical symptoms (fever, pain, pollakiuria, dysuria) and/or laboratory results (ultrasonographic signs of pyelonephritis or bacteremia) suggestive of UTI, or with polymicrobial bacteriuria with three or more pathogens suggestive of contaminated samples as well as carriers of urinary tract catheters/urethral stents were excluded. Episodes of asymptomatic bacteriuria occurring within 1 month of an acute rejection were excluded.

The physician in charge freely decided whether or not to treat the episode as well as the type and length of antibiotics.

Definitions

Following international definitions of bacteriuria and pyuria [1, 12], we classified the different episodes of asymptomatic bacteriuria in four distinct categories:

Type I: high-grade bacteriuria (≥10<sup>5</sup> cfu/mL) with pyuria (≥10 white blood cell (WBC)/field),

Type II: high-grade bacteriuria without pyuria (<10 WBC/field),

Type III: low-grade bacteriuria (<10<sup>5</sup> cfu/mL) with pyuria and

Type IV: low-grade bacteriuria without pyuria.

An episode was only considered successfully treated if pyuria and bacteriuria disappeared at the following control and there was no recurrence of bacteriuria with the same pathogen during a period of 3 weeks. A negative control culture (microbiological cure) was defined as a control culture with <10<sup>3</sup> cfu/mL.

Asymptomatic bacteriuria (whatever type) found at the control following an initial episode, whether treated or not, was not considered a new episode. Two episodes in a single patient were only considered distinct if the following two conditions were satisfied:

1. both episodes had to be at least 3 weeks apart in the absence of antimicrobial therapy,

2. both episodes had to be separated by at least one normal control urine analysis (absence of pyuria) and a sterile urine culture.

Laboratory investigations

Urine analysis with microscopic examination and urine culture were obtained routinely from every patient during their scheduled follow-up visits (once a week during the first 2 months after transplantation; twice a month during the next 3 months; once every 3 weeks for the following 2 months and once a month thereafter), as well as when clinical symptoms suggested an UTI. The urine samples were collected following a clean catch protocol.
E. faecalis and E. coli were identified at the Central Laboratory of Bacteriology via standard clinical microbiology methods. The antimicrobial susceptibility was determined by the disk diffusion method according to the latest available CLSI guidelines [14].

Statistical analysis

Each episode of bacteriuria was considered distinct and no distributional assumptions were made, we used the Mann–Whitney U-test to compare means. Two-sided Fisher’s exact tests were used to analyse differences between group proportions. Statistical significance was claimed for P ≤ 0.05 (two sided). Statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL).

Results

General outcome

None of the episodes was followed by an acute rejection in the next month or evolved toward chronic pyelonephritis. Nine patients (12%) died during the study period, none of the deaths was secondary to a URI (Table 1). Four patients (5%) developed graft failure due to chronic rejection.

Types of URI and colonization episodes

Asymptomatic bacteriuria was a frequent and recurrent event as 334 distinct episodes occurred in the 77 patients culture-positive patients (4.4 episodes/patient), including 52 Type I, 85 Type II, 36 Type III and 161 Type IV episodes (Figure 1, Table 2). All 77 patients developed more than two distinct episodes of asymptomatic bacteriuria. There was no link between types of previous episodes and types of succeeding episodes. The mean time between distinct episodes was 2.3 months. The median time from transplantation to asymptomatic bacteriuria was similar for Types III and IV episodes (3.2 and 3.7 months, respectively), whereas Types I and II episodes tended to develop later (7.8 and 4.8 months, respectively) (Table 2).

Microbiology

E. faecalis was isolated slightly more frequently in all types of asymptomatic bacteriuria (62% of Type I, 58% of Type II, 58% of Type III and 66% of Type IV episodes) (Table 2). Types I, II and IV episodes due to E. faecalis occurred earlier than those due to E. coli (mean months: 8.3 versus 19.7, 5.7 versus 16.7, 8 versus 14.5; P < 0.05). None of the E. faecalis isolates was vancomycin resistant. Most E. coli isolates were TMP–SMX resistant. No difference in progression to symptomatic UTI was detected between both pathogens (E. coli, 1 of 209, versus E. faecalis, 3 of 127; P = 0.15).

Types and lengths of antimicrobial treatments

Sixty-two per cent Type I episodes were treated, as compared to 45% Type II, 36 % Type III and 11% Type IV episodes (Figure 1). All 77 patients experienced at least one treated and one untreated episode. We observed no link between treatment of previous episodes and treatments of succeeding episodes. Mean treatment durations for Type I episodes were 12.2 days, respectively, as compared to 11.5, 10.4 and 11.4 for Types II, III and IV episodes, respectively (Table 2). No significant differences were noted in treatment durations between E. coli and E. faecalis bacteriuria. E. faecalis bacteriuria was treated with either amoxicillin or amoxicillin–clavulanate. E. coli episodes were treated with ciprofloxacin, norfloxacin, amoxicillin, amoxicillin–clavulanate or fosfomycin, depending on the result of the antimicrobial susceptibility test. Adequacy of antimicrobial treatments exceeded 95%.

Table 2. Microbiology and characteristics of 334 episodes of asymptomatic bacteriuria

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of episodes</td>
<td>52</td>
<td>85</td>
<td>36</td>
<td>161</td>
</tr>
<tr>
<td>E. coli episodes (n = 127)</td>
<td>20</td>
<td>36</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>E. faecalis episodes (n = 209)</td>
<td>32</td>
<td>49</td>
<td>21</td>
<td>106</td>
</tr>
<tr>
<td>Median time (months) from transplantation to episode and IQR</td>
<td>7.8 (1.8–21.1)</td>
<td>4.8 (1.1–13.9)</td>
<td>3.2 (1.4–8.1)</td>
<td>3.7 (1.1–12.5)</td>
</tr>
<tr>
<td>Mean duration of treatment (days) and total range</td>
<td>12.7 (2–40)</td>
<td>11.5 (1–30)</td>
<td>10.4 (3–15)</td>
<td>11.4 (3–30)</td>
</tr>
</tbody>
</table>

*IQR, interquartile range.*
Outcome of treated bacteriuria

None of the 101 treated episodes progressed toward symptomatic UTI or to a bacteriuria of another type according to our classification. Among the 32 treated Type I episodes, 2 episodes were followed by persistent Type I asymptomatic bacteriuria with the same pathogen (Table 3). Only 11 (29%) of the 38 treated Type II episodes were followed by sterile control urine cultures defining microbiological cure (Table 3). In the other 27 episodes, the control culture showed a persistent Type II bacteriuria, of which 13 episodes were due to the original pathogen. Strikingly, in eight of these episodes, the initially susceptible pathogen had become resistant to the given antimicrobial treatment. In the remaining 14 episodes, the control culture grew a new pathogen resistant to the initial antimicrobial treatment. Of the 13 treated Type III episodes, only 5 (39%) were followed by a sterile control culture. After treatment completion, the original pathogen grew again in the control cultures in three episodes, and in one of these, the initial pathogen had become resistant (Table 3). In five episodes, the control culture grew a new pathogen resistant to the preceding antimicrobial therapy. Of the 18 treated Type IV episodes, only 9 (50%) had sterile control cultures. In five episodes, the control urine culture remained positive for the initial pathogen, and in two of these episodes, the pathogen had acquired resistance. In four episodes, the control cultures were positive for a new resistant pathogen (Table 3). Therefore, only 55 of the 101 (55%) treated episodes were followed by a sterile control culture.

Outcome of untreated bacteriuria

Only 4 of the 233 (2%) untreated episodes progressed toward symptomatic UTI, including 1 Type I (E. coli) and 3 Type IV episodes (2 E. coli and 1 E. faecalis). All these events responded to subsequent antimicrobial therapy without further complications (Table 4). None of the 70 untreated Types II and III episodes were complicated by symptomatic UTI. Surprisingly, for 15 of the 20 (75%) untreated Type I episodes, the initial pathogen could not be isolated in the control urine culture. Similarly, for 23 of the 47 (49%) untreated Type II episodes, the control urine culture was negative for the initial pathogen. The control culture of nine of the 23 (39%) untreated Type III episodes was negative for the initial pathogen. Two untreated Type III episodes (9%) progressed into Type I episodes (Table 4). In 91 of the 143 (65%) untreated Type IV episodes, the initial pathogen spontaneously cleared. Four (3%) Type IV episodes progressed into Type II episodes. Therefore, spontaneous bacterial clearance was observed in 138 of 233 (59%) untreated episodes.

Outcome of treated versus untreated

We observed no differences when comparing progression toward symptomatic UTI between all treated and untreated episodes (0/101 versus 4/233, P = 0.32). Spontaneous clearance of the initial pathogen in all untreated episodes was as frequent as microbiological cure of treated episodes (138/233 versus 55/101, P = 0.47). Sterile control cultures tended to be more frequent in untreated as compared to treated Type I episodes (30/32 versus 15/20, P = 0.09) and tended to be more frequent in untreated than treated Type II episodes (23/47 versus 11/38, P = 0.08).

Discussion

Asymptomatic bacteriuria occurring in non-RTR is classified as urinary tract colonization that does not require treatment
following international guidelines [12]. Indeed, antibiotic treatment does not reduce the risk of subsequent UTI, is often unable to eradicate the colonizing organism and frequently leads to the selection of resistant organisms [12, 15, 16]. However, it is a common belief that asymptomatic bacteriuria in RTR has a different clinical significance, especially during the first month post-transplantation because the allograft is particularly susceptible to injuries at this time [13]. Underlying diseases such as advanced diabetic neuropathy, combined with denervation of the allograft and immunosuppressive medications, especially corticosteroids, affect the reliability of clinical symptoms [1]. This population is not only more prone to complications of UTI because of an incidence of reflux as high as 50% [17], but acute pyelonephritis in RTR also represents a risk factor for long-term impairment of allograft function [18]. Moreover, asymptomatic bacteriuria itself has been suggested to cause subclinical damage to the allograft due to inflammation, as increased IL-8 levels have been measured during such episodes in RTR [19]. However, this was not associated with a reduced graft function during a 1-year follow-up. Most studies that investigated the importance of bacteriuria in RTR were uncontrolled [20–22]. As a consequence of a high incidence of severe UTI with significant mortality and graft loss, several authors suggested antimicrobial prophylaxis. Indeed in observational studies, the UTI rates dropped at the time TMP–SMX was introduced for the prophylaxis of pneumocystis pneumonia [23, 24]. However, no study analysed the outcome of untreated versus treated asymptomatic bacteriuria in the post-transplant period, and there is conflicting evidence that treating asymptomatic bacteriuria could preserve allograft function [1, 25].

The fear of serious complications must be balanced against the consequences of repeated exposure to antimicrobial treatments, which include selection of resistant bacteria (methicillin-resistant Staphylococcus aureus, extended-spectrum Beta-lactamases-producing Gram-negative bacilli and vancomycin-resistant enterococi) [5, 26] and yeasts, as well as elevated costs and drug-mediated side effects.

In this retrospective study, we analysed the outcome of 101 treated and 233 untreated asymptomatic bacteriuria, caused by either E. coli or E. faecalis, in 77 RTR that occurred later than 1 month post-transplantation. We classified these episodes into four categories depending on objective laboratory results (magnitude of bacteriuria and pyuria) in order to identify potential subgroups with different outcomes. Episodes due to E. faecalis tended to be more frequent and occurred earlier than those due to E. coli. This probably reflects the protective effect against E. coli of the TMP–SMX chemoprophylaxis routinely administered during the first 6 months after transplantation. None of the treated and untreated episodes was followed by acute rejection or chronic pyelonephritis. Symptomatic UTI within 1 month of asymptomatic bacteriuria was a rare event that occurred only after four untreated episodes and we observed no difference in progression toward symptomatic UTI between treated and untreated episodes. This suggests that in our population restricting antibiotic treatment was safe and did not expose these patients to a higher risk of early infectious complications.

Spontaneous bacterial clearance was a frequent event occurring in 59% of all untreated episodes. In contrast, the microbiological benefit of antimicrobial treatment was low as bacteriuria persisted in 45% of all treated episodes. Antibiotics were not only often unable to eradicate the initial pathogen but also frequently selected resistant bacteria. Therefore, when all episodes were analysed together, resolution of bacteriuria was not more frequent in treated as compared to untreated episodes (P = 0.47). These findings are again similar to those described in non-RTR, especially spinal cord injury patients, where treatment of urinary tract colonization has been associated with various bacterial resistance without clinical benefit [15, 16]. Our study did not identify clear differences between the four subcategories based on objective laboratory results (quantitative urinary culture and sediment). However, for Type I (high-grade bacteriuria and pyuria) episodes, treated bacteriuria tended to be followed more frequently by negative control cultures than untreated episodes (P = 0.09). In contrast, for Type II episodes (high-grade bacteriuria with no significant pyuria) control cultures tended to be more frequently negative in untreated than treated episodes (P = 0.08). These trends point toward a potential value of pyuria in distinguishing episodes with high-grade bacteriuria that might benefit from treatment.

Our retrospective study presents important limitations, in particular a possible patient selection bias. Although we used a strict time frame and objective microbiological and laboratory criteria, we cannot exclude that some episodes were not completely independent. However, all episodes were distinct and could be analysed for their short-term outcome; resolution or not of bacteriuria. Also, the decision on whether or not to treat might have been influenced by different co-morbidities as well as variations in provider practice. However, while these factors clearly limit direct comparison between treated and untreated groups, they could not influence the good outcome of the untreated and the rather disappointing microbiologic evolution of the treated groups. Another limitation is our choice to restrict the analysis to E. coli and E. faecalis bacteriuria and to episodes occurring <1 month post-transplantation. These restrictions were based on the potential hypersusceptibility of the allograft early after transplantation, and the fact that these two pathogens accounted for >50% of all episodes. Including episodes caused by less frequent pathogens with significant differences in virulence such as Pseudomonas aeruginosa or Staphylococcus aureus could potentially dilute the observations. As a consequence, we cannot exclude that outcome of early untreated asymptomatic bacteriuria as well as untreated bacteriuria due to other pathogens might be different. Also, our data does not allow for the exclusion of a potential impact of not treating asymptomatic bacteriuria on long-term renal function. Indeed as all other patients, the four patients who developed chronic rejection had presented a mixture of several distinct episodes of treated and untreated asymptomatic bacteriuria, precluding the analysis of any potential link.

Our data suggests that similarly as in non-RTR not all episodes of asymptomatic bacteriuria in RTR should be treated with antibiotics. Distinctions between UTI that require antibiotic treatment and colonization that can be carefully watched without immediate treatment might
avoid selecting resistant pathogens that render treatment of real infections more difficult. Our retrospective study needs confirmation by a prospective placebo-controlled randomized trial. Such a study should allow designing evidence-based treatment guidelines of asymptomatic bacteriuria in RTR, based on objective data namely quantitative urine culture and sediment, avoiding both unacceptable clinical risks and unnecessary exposure to repeated antimicrobial agents.

Acknowledgements. E.B.E.A. was supported by a research grant from the Department of Medicine of the University Hospital Geneva.

Conflict of interest Statement. None of the authors has any commercial association that might pose a conflict of interest with this manuscript. Results of this paper have not been published previously except in abstract form.

References


Received for publication: 7.5.10; Accepted in revised form: 22.3.11