Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Antananarivo, Madagascar

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Background: Urinary tract pathogens obtained from patients in Madagascar are becoming increasingly resistant to commonly used antibiotics that are readily available at a low price. This poses a real problem for the treatment of community-acquired urinary tract infections (UTIs) in Madagascar.

Objectives: To obtain data on the pathogens responsible for community-acquired UTIs in Antananarivo and on their susceptibility patterns to the antimicrobial agents that are currently used to treat UTIs.

Methods: We conducted a retrospective study on bacteria isolated from the urine of patients at the Institut Pasteur of Madagascar between January 2004 and April 2006.

Results: We isolated 903 pathogens from 673 women and 213 men. The most commonly isolated bacteria were Escherichia coli (607 strains), Klebsiella pneumoniae (87 strains), Staphylococcus aureus (35 strains) and Proteus mirabilis (32 strains). Seventy-seven per cent of Gram-negative bacilli were resistant to amoxicillin, 65.7% were resistant to trimethoprim/sulfamethoxazole and more than 15% were resistant to ciprofloxacin. Strains were rarely resistant to more expensive antibiotics (ceftriaxone 5.9%, fosfomycin 4.6%). Most bacteria showed intermediate susceptibility to nitroxolin. Resistance rates of E. coli to ceftriaxone and gentamicin increased significantly between 2005 and 2006, due to the increase in strains harbouring an extended-spectrum β-lactamase. Gram-positive bacteria, Streptococcus and Staphylococcus spp. were rarely resistant, but 9.5% of streptococci were resistant to penicillin A and 8% of staphylococci were resistant to oxacillin.

Conclusions: The rate of amoxicillin- and trimethoprim/sulfamethoxazole-resistant Enterobacteriaceae implies that another antibiotic should be used for empirical treatment and that there is a need for new generic drugs in developing countries, especially in Madagascar.

Keywords: susceptibility testing, out-patients, UTIs

Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections encountered by both general practitioners and hospital doctors. In almost all cases, treatment must be initiated before the final bacteriological results are available. Therefore, studies to increase our knowledge about the types of pathogens responsible for UTIs and their resistance patterns to antibiotic drugs are very important to help clinicians choose the right empirical treatment.

Madagascar is one of the poorest countries in the world and the main part of the population can only afford generic drugs. Amoxicillin and trimethoprim/sulfamethoxazole are the major antibiotics used, but ciprofloxacin and gentamicin are also available at a low price. No data concerning the antimicrobial resistance of bacteria isolated from UTIs in Madagascar have been published to date.

We obtained data on the pathogens responsible for community-acquired UTIs in Antananarivo and on their susceptibility patterns to the antimicrobial agents that are currently used to treat UTIs. Our ultimate aim was to advise physicians on the first line of treatment for UTIs in Antananarivo and to advise the health authorities about the antibiotics that should be available at a low price in Madagascar.

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Materials and methods

Bacterial isolates

We carried out a retrospective study on all of the bacterial strains isolated from the urine of out-patients who attended the Institut Pasteur of Madagascar (IPM) with a suspected UTI between January 2004 and April 2006. All samples were collected at IPM. Only patients who had pyuria (>10 white blood cells/µL) and significant bacteriuria (>10^7 cfu/mL) were included in the microbiological analysis. Only one specimen per patient was included in the study.

The bacteria were identified by Gram staining and standard microbiological techniques.

Antibiotic susceptibility testing

Susceptibility to antibiotics was assessed by the disc diffusion technique on Mueller–Hinton agar (MH) or MH + 5% sheep blood, as recommended by the Antibiogram Committee of the French Microbiology Society (ACFMS). Antibiotic discs were obtained from Bio-Rad, Marne la Coquette, France. The antibiotics tested were recommended by the ACFMS. After 24 h at 37°C, the zone of inhibition was measured. To detect extended-spectrum β-lactamases (ESBLs), discs of ceftazidime and ceftriaxone were placed 30 mm from an amoxicillin/clavulanate (20/10 μg) disc. Enhancement of the zone of inhibition between the clavulanate disc and any one of the third-generation cephalosporin discs indicated the presence of an ESBL. The distance between the discs could be reduced when the synergy was not easily observed as in cephalosporinase-producing strains. Escherichia coli ATCC 25922, Staphylococcus aureus ATCC 25923 and Pseudomonas aeruginosa ATCC 27853 were used as controls.

Socio-economic background

Most of the patients attending IPM belong to middle or upper classes of Antananarivo. About 40% of the patients are supported by their employers (government or private societies), and 50% pay for themselves. About 5% are strangers with high incomes and ~5% are from the low classes but are supported by associations. The antibiotics can be bought in hospitals or pharmacies. However, some are available in markets and their reliability cannot be guaranteed. Most of the patients attending IPM buy the antibiotics in hospitals or pharmacies.

Epidemiological data

The influence of previous UTI or antibiotic treatment was studied for 149 patients presenting a UTI due to E. coli from April 2004 to August 2005. After informed consent was obtained, patients answered a questionnaire concerning these risk factors. Patients who had been hospitalized during the previous month were not included. This epidemiological study was approved by the ethical committee of the Ministry of Health of Madagascar.

Data analysis

Patient (age, sex, date of isolation) and microbiological data were entered using the Osiris Automated Susceptibility System, Bio-Rad, Marne la Coquette, France. Data concerning risk factors were entered on EpiInfo®. All data were analysed using EpiInfo® and SPSS® statistical software.

Results

Pathogens were isolated from 886 of the 6884 patients who submitted a urine sample (12.9%). Among them, 673 were women and 213 were men (mean age 33.9 years, range 0–83 years, sex ratio 0.32). Seventeen patients presented a co-infection and therefore 903 strains were isolated. More than 85% of isolates were Enterobacteriaceae: E. coli (67.2%), Klebsiella pneumoniae (9.6%), Proteus mirabilis (3.6%) and other Enterobacteriaceae (5.5%). Other Gram-negative bacteria (Pseudomonas spp. and Acinetobacter spp.) accounted for 2.2% of the isolates. Only 11.4% of the isolates were Gram-positive: S. aureus (3.9%), Enterococcus faecalis (2.8%), streptococci (3.2%) and coagulase-negative staphylococci (CoNS) (1.5%). Candida albicans was isolated from five individuals. There was no significant difference concerning the species according to age classes or gender.

E. coli was susceptible to many drugs, but about 74% of strains were resistant to amoxicillin and ticarcillin and 70% to trimethoprim/sulfamethoxazole (Table 1). About half of the other Enterobacteriaceae were also resistant to trimethoprim/ sulfamethoxazole and 80% produced a β-lactamase, which confers resistance to amoxicillin. About 85% of strains of Enterobacteriaceae were susceptible to fluoroquinolones and most strains were susceptible to third-generation cephalosporins (Table 1). Resistance to third-generation cephalosporins was mostly due to the presence of ESBLs. ESBLs were found in 29 Enterobacteriaceae (20 E. coli, 5 K. pneumoniae, 2 Enterobacter cloacae, 1 Enterobacter aerogenes and 1 Citrobacter freundii). One of the most effective drugs remained ciprofloxacin (~85% of strains were susceptible). Gram-positive cocci were susceptible to the major drugs used on these species; only 8% of the staphylococci were resistant to oxacillin (2 of 35 strains of S. aureus and 2 of 15 strains of CoNS), and 9.5% of the streptococci were resistant to amoxicillin. More than 80% of the staphylococci were susceptible to fluoroquinolones (33 of 35 strains of S. aureus and 9 of 15 strains of CoNS), but only 66% to trimethoprim/sulfamethoxazole (24 of 35 strains of S. aureus and 9 of 15 strains of CoNS); all Gram-positive bacteria were susceptible to glycopeptides. Nearly 94% of the strains isolated were susceptible to fosfomycin.

Resistance rates of E. coli to ceftriaxone and gentamicin increased significantly between 2005 and 2006: 3.2% versus 8.8% and 8% versus 16.7%, respectively. This was due to the significant increase in strains harbouring an ESBL. Indeed, in 2004, four strains of E. coli among 244 presented an ESBL, eight among 249 in 2005 and eight among 114 in 2006 (P = 0.03).

Strains of E. coli isolated in patients aged 65 years or more were significantly more resistant to third-generation cephalosporins (P = 0.04) and to ciprofloxacin (P < 0.01). There was no difference in the resistance pattern according to gender.

Among 149 patients with a UTI due to E. coli that were studied concerning their risk factors, 34 (22.8%) and 19 (12.7%) declared an antibiotic treatment or a UTI during the previous month, respectively. E. coli strains isolated from patients who received a previous antibiotic treatment were more resistant to amoxicillin although not significantly (P = 0.057). No other significant difference was found.

Discussion

This is the first study to evaluate the susceptibility patterns of bacterial strains isolated from community-acquired UTIs in Antananarivo, Madagascar. This study provides valuable laboratory data and allows comparison of the situation in
Table 1. Susceptibility of Enterobacteriaceae isolated from community-acquired UTIs to various antimicrobial agents.

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>E. coli (n = 607)</th>
<th>Other Enterobacteriaceae (n = 168)</th>
<th>All Gram-negative bacilli (n = 794)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>resistant (%)</td>
<td>intermediate (%)</td>
<td>susceptible (%)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>73.8</td>
<td>3.3</td>
<td>22.9</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>11.5</td>
<td>43.7</td>
<td>44.8</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>73.8</td>
<td>3.3</td>
<td>23.4</td>
</tr>
<tr>
<td>Cefalotin</td>
<td>19.6</td>
<td>35.9</td>
<td>44.5</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>16.4</td>
<td>36.9</td>
<td>47</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>31.5</td>
<td>17.4</td>
<td>50.1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>73</td>
<td>8.8</td>
<td>83.4</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>3.9</td>
<td>3.4</td>
<td>92.7</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>16.4</td>
<td>3.4</td>
<td>95.3</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.6</td>
<td>1.7</td>
<td>98</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>16.4</td>
<td>2.2</td>
<td>95.6</td>
</tr>
<tr>
<td>Nitrofurantion</td>
<td>0.2</td>
<td>0.3</td>
<td>98.8</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>0.2</td>
<td>0.3</td>
<td>98.8</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>69.5</td>
<td>26.9</td>
<td>3.6</td>
</tr>
</tbody>
</table>
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Antananarivo with that in other countries. Unfortunately, very few data exist concerning UTIs in developing countries, especially in Africa. In our study, E. coli was the most common pathogen isolated. This corresponds to the data obtained by other groups;4,8 K. pneumoniae was the second most common pathogen (9.6%). This percentage is higher than that observed in many countries,4,6 but lower than reported from the Sudan or the Central African Republic.7,8

The main differences between our results and the results of studies conducted in developed countries were the resistance patterns of Enterobacteriaceae. In our study, a higher proportion of strains were resistant to amoxicillin (~80%) and trimethoprim/sulfamethoxazole (~60%) than in studies conducted in developed countries (between 30% and 45% were resistant to amoxicillin and between 20% and 40% were resistant to trimethoprim/sulfamethoxazole).4,6 This phenomenon is similar to that observed in other African countries such as the Sudan or the Central African Republic.7,8 These antibiotics are the most commonly used ones in Madagascar because they are cheap and easy to administer. However, resistance to trimethoprim/sulfamethoxazole is lower than in the Central African Republic. This may be due to the fact that this drug is used in the prevention of opportunistic infections associated with HIV and that the prevalence of HIV in Central African Republic is much higher than that reported in Madagascar.9,10 The extensive use of these drugs explains the high selection pressure for resistant bacteria. Conversely, strains are rarely resistant to more expensive drugs.

However, the resistance to third-generation cephalosporins and ciprofloxacin was significantly higher in patients aged 65 years or more. This is probably due to the fact that they are more likely to have received repeated antibiotic treatments and to have been hospitalized more frequently than younger patients. Moreover, the increasing resistance rate to third-generation cephalosporins in E. coli between 2005 and 2006 is striking. This phenomenon is due to the increase of ESBLs. This increase of ESBLs in community-acquired infection is worrying, since the use of third-generation cephalosporins is rather rare in Antananarivo. An epidemic of ESBLs can be feared when this use becomes more frequent.

For cost reasons, physicians rarely request bacteriological examinations of urines. This phenomenon may have introduced bias in our study and led to overestimation of the prevalence of resistance to amoxicillin and trimethoprim/sulfamethoxazole if a large number of patients attended IPM after the failure of empirical treatment. However, among 149 patients who answered a questionnaire only 12.7% declared a previous UTI; and no significant difference in the resistance pattern of E. coli strains was found between patients declaring previous UTI or antibiotic treatment and those who did not. Therefore the rate of resistance observed in our study is probably realistic.

This study highlights the need for the development of new generic drugs, otherwise the resistance to ciprofloxacin, the cheapest of the drugs that remain highly efficient, will increase rapidly in the near future.

This retrospective study should be followed by a multicentre study on antimicrobial resistance in Antananarivo and other regions in Madagascar to determine whether the resistance patterns and the increase in resistance to third-generation cephalosporins are similar.

Acknowledgements

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Transparency declarations

None to declare.

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