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Antimicrobial resistance in Cairo, Egypt 1999–2000: a survey of five hospitals

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Antimicrobial resistance among bacterial pathogens is a global problem, but in Egypt data are sparse. We reviewed the antimicrobial susceptibility patterns of bloodstream isolates of Gram-positive cocci and Gram-negative bacilli in five hospitals in Cairo, Egypt, from 1999 to 2000. In addition, susceptibilities of non-bloodstream isolates of *Streptococcus pneumoniae* and *Enterococcus* spp. were analysed. High rates of resistance were found in most of the bacteria studied. In the hospitals, a variety of methods were used for identification and susceptibility testing, but in the laboratories quality controlled strains were utilized routinely, to ensure accurate performance of the assays. Only 29% of *Staphylococcus aureus* isolates and 23% of coagulase-negative staphylococcal isolates were oxacillin susceptible. Both groups of staphylococci were also highly resistant to erythromycin, co-trimoxazole, clindamycin and doxycycline; all isolates were susceptible to vancomycin. Susceptibility of *S. pneumoniae* isolates to penicillin, ceftriaxone and fluoroquinolones was 63%, 84% and 82%, respectively. Vancomycin susceptibility of the enterococci was 96%; susceptibility to high-level gentamicin and streptomycin was 54% and 48%, respectively. Resistance to most relevant antimicrobials was commonplace among the Gram-negative bacilli; however, most remained susceptible to imipenem. The percentage of bloodstream isolates of *Escherichia coli* susceptible to common antimicrobial agents was as follows: ampicillin (6%), ampicillin–sulbactam (38%), co-trimoxazole (38%) and aminoglycosides (52%). The susceptibility of isolates of *E. coli*, *Klebsiella* and *Enterobacter* spp. to ceftazidime was 62%, 40% and 46%, respectively. This suggests a potentially high rate of extended-spectrum β-lactamase (ESBL) and/or Amp-C enzyme production. These results call for a nationwide surveillance programme to monitor microbial trends and antimicrobial resistance patterns in Egypt.

Keywords: resistance, Egypt, bacterial susceptibility testing, Gram-negative bacilli, Gram-positive cocci

Introduction

Infections caused by resistant pathogens result in significant morbidity and mortality, and contribute to escalating healthcare costs worldwide. Despite the availability of newer antibiotics, emerging antimicrobial resistance has become an increasing problem in many pathogens throughout the world.[1–3] For practising physicians, clinical microbiologists and public health officials, knowledge of local antimicrobial resistance patterns is essential to guide empirical and pathogen-specific therapy. This information is also critical for optimal decisions regarding hospital formulary and infection control policies, for the rational formulation of public healthcare policies, and national and international research agendas in this area. Unfortunately, data regarding endemic antimicrobial resistance are unavailable in many parts of the world, especially from areas where over-the-counter antibiotic use is common.

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Few papers have examined endemic antimicrobial resistance in Egypt, although several reports have studied the occurrence and resistance patterns of specific respiratory and enteric pathogens,[4–6] and a few small, short-term studies from individual institutions have been reported in Egyptian medical journals.[7,8] This study was therefore undertaken to identify regional endemic antimicrobial resistance patterns among common bacterial isolates from patients in five hospitals in Cairo.

Materials and methods

Study design

This was a retrospective, multicentre study, conducted utilizing microbiology laboratory records from 1 July 1999 to 30 June 2000, from five hospitals in the greater Cairo region. These hospitals included Cairo University Pediatric Hospital (CUPH; 350 beds), Dar Al Fouad Hospital (DAF; 40 beds), Manial University Hospital (MUH) of Cairo University (1200 beds), Manial Specialized Hospital of Cairo University (MSUH; 300 beds) and the Specialized Hospital of Ain-Shams University (AS; 800 beds). These hospitals, collectively, admit patients from all socioeconomic strata from Cairo and the surrounding rural areas, although patient populations vary among individual institutions.

Microbiology data

Microbiology records were reviewed by two of the authors (A.E.K. and H.B.). The isolates studied were confined to unrelated first isolates from different patients, and did not include multiple isolates from the same patient. All isolates were recovered from blood cultures; some coagulase-negative staphylococcal isolates were single isolates from blood cultures and thus of uncertain clinical significance. Specific antimicrobials tested varied from one institution to another. Information regarding the isolate, its source and antimicrobial susceptibility profile was collected and recorded. Data from different institutions were pooled. Because of lack of medical records, information regarding the clinical significance of each isolate and whether infection was community- or hospital-acquired was not available; however, by restricting our analysis to blood isolates and isolates of enterococci and pneumococci from other sites, we attempted to increase the likelihood of the clinical significance of most isolates other than coagulase-negative staphylococci.

Organism identification and susceptibility testing

All isolates were identified at the participating institution by standard laboratory methods.[9,10] Confirmation of species identification of Gram-negative bacilli was performed with Microscan Walkaway System (Dade MicroScan, Inc., W. Sacramento, CA, USA), Sensititre (TREK Diagnostics Inc., Westlake, OH, USA) or BBL Crystal (Becton Dickinson Microbiology Systems, Sparks, MD, USA) products. Each laboratory performed susceptibility testing according to their own standardized techniques based on current NCCLS guidelines.[11,12] The Kirby–Bauer disc diffusion method, which is the predominant method employed in Egypt, was used at CUPH, DAF and MUH. In MSUH, the Sensititre semi-automated instrument (TREK) was used, and the Micoscan Walkaway (Dade) automated system was employed at AS. Quality control strains were utilized routinely in all laboratories to ensure accurate performance of the assays. For data analysis, resistance included combined, intermediate and resistant results.

Results

Sources of isolates

One thousand five hundred and twenty-nine isolates were recovered from blood cultures of patients over the course of this 1 year retrospective study. An additional 51 isolates of *Streptococcus pneumoniae* and 69 of *Enterococcus* spp. over the same period from sites other than blood were analysed.

Resistance

As can be seen in Table 1, 442 staphylococci were isolated from blood cultures. The rate of oxacillin resistance was similar among both *Staphylococcus aureus* and coagulase-negative staphyloccal isolates, at 71% and 77%, respectively. The non-susceptibility to ciprofloxacin was 49% and 50%, respectively, for *S. aureus* and coagulase-negative staphylo-

Table 1. Percentage susceptibility of bloodstream isolates of Gram-positive cocci

	Staphylococcus aureus (% S)	Coagulase-negative staphylococci (% S)
Isolates (*n*)	77	365
Cefazolin	29	23
Ceftriaxone	29	23
Chloramphenicol	53	47
Ciprofloxacin	51	50
Clindamycin	64	55
Co-trimoxazole	66	29
Doxycycline	70	58
Erythromycin	51	51
Gentamicin	43	55
Oxacillin	29	23
Penicillin	1	3
Rifampicin	88	84
Vancomycin	100	100

Table 2. Percentage susceptibility of non-bloodstream isolates of Gram-positive cocci

	S. pneumoniae (% S)	*Enterococcus* spp. (% S)
Isolates (*n*)	51	69
Ceftriaxone	84	
Chloramphenicol	82	80
Ciprofloxacin	82	
Clindamycin	49	
Co-trimaxozole	63	
Doxycycline	96	
Erythromycin	45	
Gentamicin	43	
Gentamicin (HL)		54
Penicillin	63	
Streptomycin (HL)		48
Vancomycin	100	96

HL, high-level; provides for detection of high-level aminoglycoside resistance.

coccal isolates. Higher rates of susceptibility were demonstrated for *S. aureus* as compared with coagulase-negative staphyloccal isolates versus clindamycin (64% and 55%), co-trimoxazole (66%% and 29%) and doxycycline (70% and 58%). All isolates of staphylococci were susceptible to vancomycin. Percentage susceptibilities of non-bloodstream isolates of *Streptococcus pneumoniae* and *Enterococcus* spp. are shown in Table 2.

There were 532 isolates of *Enterobacter* spp. and 303 of *Pseudomonas aeruginosa*, as compared with a total of 252 for all other Gram-negative bloodstream isolates. Susceptibility to imipenem for the Enterobacteriaceae was >98.7%. For *P. aeruginosa*, 98.7% were susceptible to imipenem, as compared with only 89.7% of the *Acinetobacter* spp. Susceptibility to ciprofloxacin was >79.2% for all groups tested. Ampicillin–sulbactam and cefazolin demonstrated a 38% and 40% susceptibility, respectively, versus *E. coli*, but had 100% resistance versus the other Gram-negative bacilli. Ceftazidime and cefotaxime susceptibilities were <72% for all groups (Table 3).

Discussion

The striking finding in this 1 year retrospective study at five major teaching hospitals in Cairo is the high degree of antimicrobial resistance among the isolates studied. Our isolates represented both nosocomial- and community-acquired pathogens, and were collected from five different hospitals in Cairo. Although data stratified by hospital are not presented in detail, resistance among Gram-positive cocci and Gram-negative bacilli was widespread between the participating hospitals. We do not have epidemiological or clinical data to evaluate further the extent to which these resistance patterns reflect endemic antimicrobial resistance within the community, versus nosocomial spread of resistant organisms within and between various hospitals. But we know that each facility had its own infection control programme. Nevertheless, we believe that these data highlight the fact that widespread antimicrobial resistance exists in Cairo.

Staphylococcal isolates were highly resistant to all antimicrobials tested, except vancomycin. Nearly five times as many coagulase-negative staphylococci were isolated, as

Table 3. Percentage susceptibility of bloodstream isolates of Gram-negative bacilli

	E. coli (% S)	*Klebsiella* spp. (% S)	*Enterobacter* spp. (% S)	*Citrobacter* spp. (% S)	*P. aeruginosa* (% S)	*Acinetobacter* spp. (% S)
Isolates	50	149	532	24	303	29
Amikacin	52	47	33	50	40	52
Ampicillin	6	0	0	0	0	0
Ampicillin–sulbactam	38	0	0	0	0	0
Aztreonam	56	36	46	76	54	52
Imipenem	100	99	99	100	99	90
Cefazolin	40	0	0	0	0	0
Cefoperazone–sulbactam	60	59	46	71	56	52
Ceftazidime	62	40	46	71	62	52
Cefotaxime–ceftriaxone	58	35	45	62	54	48
Co-trimoxazole	38	45	25	62	0	52
Ciprofloxacin	84	88	94	79	96	83
Gentamicin	52	42	30	42	31	34
Piperacillin	46	38	36	54	53	24
Tobramycin	52	42	30	42	33	45

compared with *S. aureus*. Although some of the coagulase-negative staphylococci were probably the cause of true bacteraemia, many could have represented skin contamination. Among bloodstream isolates of staphylococci, 71% of strains of *S. aureus* and 77% of strains of coagulase-negative staphylococci were resistant to oxacillin. The *S. aureus* resistance rates were higher than those in the USA and Canada, reported in the SENTRY Antimicrobial Surveillance Program, in which 26.2% of bloodstream isolates from the USA and 2.7% of similar isolates from Canada were methicillin resistant.[2] Compared with our isolates, the Canadian isolates of *S. aureus* were also more susceptible to gentamicin, fluoroquinolones, macrolides and co-trimoxazole.[2]

Resistance rates among staphylococci have been reported from other geographical areas with results similar to ours. In the study of Melo-Cristino in Portuguese hospitals, methicillin resistance was found in 48.2% of *S. aureus* isolates, and in 71–84% of coagulase-negative staphylococci, rates similar to those found in our study.[13] Among staphylococci from 19 European hospitals, methicillin resistance was found in 28% and 68% of *S. aureus* and coagulase-negative staphylococci, respectively.[14]

Penicillin resistance among our isolates of *S. pneumoniae* was comparable to other parts of the world, although higher than previous reports from Egypt.[6] In our study, 63% of isolates were susceptible to penicillin, compared with 71% in a prior study from Egypt.[6] Eighty-four per cent and 82%, respectively, of isolates were susceptible to ceftriaxone and ciprofloxacin. The high rate of resistance in our isolates is consistent with many studies. Results of the SENTRY study in the USA and Canada showed decreased susceptibility of pneumococci to penicillin, to a degree similar to our isolates. Both USA and Canadian isolates remained susceptible to fluoroquinolones (96–100%) and vancomycin (100%).[2] Fluoroquinolone resistance among pneumococci has been considered rare.[15,16] Ciprofloxacin is known to possess only borderline activity against pneumococci, as compared with the activity of other fluoroquinolones, such as levofloxacin, gatifloxacin or moxifloxacin; however, 18% is quite high.[17] Since it was the only fluoroquinolone reported in the present study, it is difficult to speculate what the level of fluoroquinolone resistance truly is versus *S. pneumoniae*. Further study is needed to define the epidemiology of these infections and what effect the high resistance of ciprofloxacin will have on the use of other more active fluoroquinolones versus *S. pneumoniae*.

In contrast to reports from many parts of the world, <5% of our enterococcal isolates were vancomycin resistant.[18,19] Our rate was similar, however, to that reported by Araj & Kanj[20] in Lebanon. Similar to other geographical areas, high levels of resistance to gentamicin and streptomycin were identified in about half of our isolates.[2]

Antimicrobial resistance among Gram-negative bacilli in our study was significant. Among isolates of *E. coli*, only 6% were susceptible to ampicillin, 38% to ampicillin–sulbactam, 38% to co-trimoxazole and 52% to the aminoglycosides. All isolates were susceptible to imipenem. *E. coli* isolates in our study were more resistant to the fluoroquinolones than those from the USA and Canada.[2]

Antibiotic resistance among isolates of *Klebsiella*, *Enterobacter*, *Citrobacter, Acinetobacter* and *P. aeruginosa* was common in the present study, and comparable to reports from other parts of the world.[21–24] Imipenem and ciprofloxacin retained activity against most of these isolates, except for *Citrobacter* and *Acinetobacter* spp. Perhaps one of the most striking findings in our study was the high level of ceftazidime and/or cefotaxime resistance among our isolates of *Klebsiella* and *E. coli.* Thirty-eight per cent of the *E. coli* isolates and 60% of *Klebsiella* spp. were ceftazidime resistant, with similar findings when compared with cefotaxime. Ceftazidime and cefotaxime resistance are markers for the presence of extended-spectrum β-lactamases (ESBLs). Aztreonam resistance is also defined by the NCCLS as a potential marker for the presence of an ESBL-producing organism; in our study, resistance to aztreonam among isolates of *E. coli* and *Klebsiella* spp. was high at 44% and 64%, respectively. Whereas we did not perform confirmation tests or genetic analyses to confirm the presence of ESBL enzymes in these isolates, the high MIC results suggest that ESBL enzymes are endemic in Cairo. Further epidemiological studies are necessary to determine whether such isolates exist in the community, or remain largely confined to tertiary hospitals where they produce nosocomial infections.

The prevalence of ESBL enzymes has been increasing in many parts of the world. Infections caused by ESBL-producing isolates are difficult to treat, because they confer resistance to all currently available β-lactam agents, except imipenem, and in some cases piperacillin–tazobactam.[24–26] In addition, ESBL production is usually associated with resistance to other classes of antimicrobial agent, such as aminoglycosides and fluoroquinolones.[27]

Enterobacter spp. were highly resistant to ceftazidime, cefotaxime and aztreonam as well in the present study. In a study published in 1998 by Jones *et al.*[25] from the USA, 33.4% of *Enterobacter* isolates were resistant, or intermediately susceptible, to ceftazidime. In a more recent study, Mathai *et al.*[28] reported that among pulmonary isolates of *Enterobacter* spp. from the USA, only 79.6% were susceptible to ceftazidime, whereas 100% remained susceptible to imipenem. These results can be explained by the high prevalence of ESBL- and AmpC-induced resistance among *Enterobacter* isolates, which render the use of third-generation cephalosporins ineffective.[29] Our data suggest the presence of similar resistance mechanisms in Egyptian isolates. We cannot explain why the number of *Enterobacter* spp. exceeded all other Entero-

bacteriaceae; however, this may be another reflection of the increased resistance among Gram-negative bacilli, since *Enterobacter* spp. are among the most resistant of the group.

The susceptibility of bloodstream isolates of *P. aeruginosa* and *Acinetobacter* spp. isolates in the present study was low to ceftazidime, piperacillin, aztreonam and aminoglycosides; however, susceptibility of isolates in our study to imipenem and ciprofloxacin was higher than in published reports from the USA.[2,22,30]

In conclusion, our data suggest that antimicrobial resistance among Gram-positive cocci and Gram-negative bacilli is common and significant in Cairo. One of the explanations for these high resistance rates could be antibiotic usage in the respective institutions. el-Teheawy *et al*.[31] in Egypt in 1988 reported that >80% of admitted patients were prescribed antibiotics, and in many cases without documented proof of infection. Among these patients, >30% received repeated courses, with no apparent reasons for doing so. Whether this would still be the practice today is unknown by the authors of the present paper.

Particularly alarming are the high rates of ceftazidime resistance among *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., which suggest the presence of ESBL and AmpC enzymes. Our results have important implications for practising physicians in the region, with regard to empirical antibiotic selection. They also have important implications for authorities involved in hospital formulary decisions, and in the development of policies regarding antibiotic utilization, infection control and public healthcare. Our results call for further epidemiological studies to define whether ESBLs are highly endemic in the community and, on a larger scale, for the implementation of a regional and nationwide surveillance system to monitor antimicrobial resistance trends in Egypt.

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