Low antibiotic resistance rates in *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella* spp but not in *Enterobacter* spp and *Pseudomonas aeruginosa*: a prospective observational study in 14 Swedish ICUs over a 5-year period


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Background: Intensive care units (ICUs) are hot zones for emergence and spread of antibiotic resistance because of frequent invasive procedures, antibiotic usage and transmission of bacteria. We report prospective data on antibiotic use and bacterial resistance from 14 academic and non-academic ICUs, participating in the ICU-STRAMA programme 1999–2003.

Methods: The quantity of antibiotics delivered to each ICU was calculated as defined daily doses per 1000 occupied bed days (DDD1000). Specimens for culture were taken on clinical indications and only initial isolates were considered. Species-related breakpoints according to the Swedish Reference Group for Antibiotics were used. Antibiotic resistance was defined as the sum of intermediate and resistant strains.

Results: Mean antibiotic use increased from 1245 DDD1000 in 1999 to 1510 DDD1000 in 2003 (P = 0.11 for trend). Of *Staphylococcus aureus*, 0–1.8% were methicillin resistant (MRSA). A presumptive extended spectrum beta-lactamase (ESBL) phenotype was found in <2.4% of *Escherichia coli*, based on cefotaxime susceptibility, except a peak in 2002 (4.6%). Cefotaxime resistance was found in 2.6–4.9% of *Klebsiella* spp. Rates of resistance among *Enterobacter* spp to cefotaxime (20–33%) and among *Pseudomonas aeruginosa* to imipenem (22–33%) and ciprofloxacin (5–21%) showed no time trend.

Conclusion: MRSA and cefotaxime-resistant *E. coli* and *Klebsiella* spp strains were few despite high total antibiotic consumption. This may be the result of a slow introduction of resistant strains into the ICUs, and good infection control. The cause of imipenem and ciprofloxacin resistance in *P. aeruginosa* could reflect the increased consumption of these agents plus spread of resistant clones.

Key words: Anti-infective agents; critical care; cross infection; multiple drug resistance.
multidrug-resistant organisms. ICUs were enrolled in ICU-STRAMA which monitored antibiotic use, antibiotic resistance and infection control practices with the use of electronic questionnaires (7). Data were fed back on a regular basis at local and regional levels together with multidisciplinary meetings that involved staff from hospital hygiene, clinical microbiology and the hospital pharmacy in addition to intensive care and infectious disease physicians (4, 7). The number of ICUs that took part in the programme has increased from 14 to 29 over the years. The purpose of the present work is to report the results from the original 14 ICUs of the first 5 years of this surveillance programme, focusing on trends in antibiotic consumption and resistance.

Materials and methods

Methods for collection and validation of data have been described in detail earlier (4, 7). Briefly, questionnaires were sent annually to the ICUs and their corresponding laboratories of clinical microbiology, hospital pharmacies and departments of infectious diseases.

Antibiotic consumption was expressed as annually updated defined daily doses (DDD) per 1000 occupied bed days (DDD_{1000}) (http://www.whocc.no/atcddd/, accessed 14/06/2007). Specimens from patients were taken for culture on clinical indications and only initial isolates were considered. Susceptibility testing was performed at the time of sampling using the standardized disc diffusion method according to the Swedish Reference Group for Antibiotics (SRGA) including species-related zone break points for the categories susceptible, intermediate and resistant (www.srga.org, accessed 2007/06/14) (8). Antibiotic resistance was defined as the sum of intermediate (I) and resistant (R) strains. Escherichia coli isolates with decreased susceptibility (I + R) to ceftaxime were defined as presumptive extended spectrum beta-lactamase (ESBL) phenotypes. Confirmation with discs or E-tests with ceftaxime^{–/–} clavulanic acid and ceftazidime^{–/–} clavulanic acid is now the recommended method for confirmation of the ESBL phenotype among E. coli and Klebsiella spp. but was not fully implemented at the beginning of this study.

Statistics

Data were analysed using the non-parametric test for trend across ordered groups and Spearman’s rank correlation using STATA/SE 9.2 (StataCorp LP, College Station, TX, USA) and SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Statistical significance was assumed if \( P < 0.05 \).

Results

Antibiotic consumption and resistance data were collected from 1999–2003 from 14 ICUs. These were located in five tertiary care academic hospitals, five district general hospitals and four local hospitals, and were mixed medical–surgical \((n = 13)\) and cardiothoracic/vascular \((n = 1)\). The median number of beds per ICU was eight \((range \ 6–12)\) and the mean number of admissions per ICU and year was 1782. Mean acute physiology and chronic health evaluation II (APACHE II) scores per unit and year were between 9.0 and 18.4 points, the overall mean \((SD)\) was 14.1 \((2.7)\). However, five ICUs did not collect APACHE scores. Mean \((SD)\) length of stay per ICU and year were 35.6 \((17.2)\) h.

Antibiotic use

Mean total antibiotic use increased from 1245 DDD_{1000} in 1999 to 1510 DDD_{1000} in 2003 \((P = 0.11\) for trend, Fig. 1). The use of three of the most common antibiotic classes increased during the study but the trends were not significant \((cephalosporines \ P = 0.06,\ carbapenems \ P = 0.26\) and fluoroquinolones \(P = 0.12)\).

Written guidelines for choice of empiric antibiotic therapy and routines for setting a preliminary date

Fig. 1. Consumption of different antibiotic classes as defined daily doses (DDD) per 1000 patient days over the 5-year period studied. Penicillins (Beta-lactamase sensitive penicillins). Note logarithmic axis. There were no statistically significant time trends.
for discontinuation of each prescribed antibiotic remained uncommon throughout the study (mean 23% and 17% of ICUs per year).

Antibiotic susceptibility
The proportion of ESBL phenotype among *E. coli* was below 2.4% except a peak in 2002, as a result of an outbreak of such strains in one ICU. The same ICU had an outbreak of ciprofloxacin-resistant *E. coli* during 2002 causing an increase in ciprofloxacin resistance rates which otherwise were below 4% (Table 1). Cefotaxime resistance was found in 2.6–4.9% of *Klebsiella* spp. The percentage of MRSA varied between 0 and 1.8. High rates of resistance among *Enterobacter* spp. to cefotaxime (20–33%), and *Pseudomonas aeruginosa* to imipenem (22–33%) and ciprofloxacin (5–21%) were found (Table 1). There were no statistically significant trends of resistance over time.

We found no relationships between consumption of carbapenems or quinolones and resistance to these drugs in *P. aeruginosa*. Correspondingly, no relationship was seen between consumption and resistance for cephalosporins in *Enterobacter* spp.

Discussion
There were three important findings in this prospective, observational study. First, antimicrobial drug consumption was relatively high during the 5-year period with every patient receiving on average 1.2 antimicrobial drugs per day in 1999 with an increasing trend to 1.5 antimicrobials per day in 2003. Second, the proportions of antibiotic-resistant *S. aureus*, *E. coli* and *Klebsiella* spp remained low in spite of the consumption of antibiotics. Third, the resistance rates among *Enterobacter* spp. to cefotaxime and *P. aeruginosa* to ciprofloxacin and imipenem remained high enough to be of concern throughout the study.

This study was done in ICUs that showed an interest in issues related to antibiotic consumption and bacterial resistance. Nevertheless, we believe that they were relatively representative of antibiotic consumption and bacterial resistance. Nevertheless, we believe that they were relatively representative of antibiotic consumption and bacterial resistance. Nevertheless, we believe that they were relatively representative of antibiotic consumption and bacterial resistance. Nevertheless, we believe that they were relatively representative of antibiotic consumption and bacterial resistance. Hence, we believe that they were relatively representative of antibiotic consumption and bacterial resistance.
reported to the Swedish Intensive Care registry. The illness severity of admissions (computed for true ICU cases, only), as reflected by APACHE II scores, was slightly greater than those of the Swedish Intensive Care Registry (mean 13.4, 25–75 percentiles: 7–19 over the past 4 years). These differences compared with national data were small enough to support our belief that the findings were reasonably representative of Swedish adult critical care.

We calculated antibiotic use as defined daily doses per 1000 occupied bed days (DDD\(_{1000}\)), as DDD is a highly standardized measure that allows comparison of antibiotic consumption between different settings and countries, as long as a common definition is also used for length of stay. Antibiotic consumption was based on the quantities of drugs delivered by local hospital pharmacies to the ICUs. Potential errors in these data, particularly delivered but not administered drugs, may have caused an overestimation of the antibiotics given to ICU patients. However, in a prevalence study of antibiotic use in 23 Swedish ICUs performed during 2 weeks in 2000, 74% of 393 patients were on antibiotics (9). When taking into account that 1 in 3 patients were treated with more than one antibiotic (9), the antibiotic consumption was almost as high as shown in this study. We found a total antibiotic consumption of >1000 DDD\(_{1000}\) such as in European and US ICUs in general (10,11), but in a Swiss ICU study lower rates were found (462 DDD\(_{1000}\) in the surgical ICU and 683 DDD\(_{1000}\) in the medical ICU) (12). The exceptionally low antibiotic use in the Swiss surgical ICU was apparently as a result of strong control efforts and aggressive diagnostic practices (12). Calculation of antibiotic consumption and benchmarking with other ICUs and hospitals may be a tool for better understanding of what drives current resistance problems at a local level and may lead to more appropriate antibiotic use (13).

We studied antibiotic susceptibility among E. coli, Klebsiella spp., Enterobacter spp., P. aeruginosa and S. aureus regardless if they were the cause of ICU-acquired infections, community acquired infections or only colonizing the patients, because these were the most frequently reported Gram-negative bacteria causing ICU-acquired infections in an earlier large European prevalence study (1). However, among Gram-positive bacteria coagulase-negative staphylococci, Enterococcus and Streptococcus spp. were at least as common as S. aureus in our study. Of these, we chose to present MRSA only because such strains represent the current challenge among antibiotic-resistant Gram-positive pathogens.

A considerable strength of this work was that susceptibility results were validated by comparison of in-house susceptibility distributions with reference distributions. Moreover, susceptibility results were controlled with the use of quality control strains according to national guidelines (www.srsga.org, accessed 14/06/2007). This highly standardized assessment of bacteria enabled comparison of data analysed by different laboratories. Another strength was that we included initial isolates of bacteria only, repeat isolates of the same species with the same antibiogram from the same patient were excluded, thus avoiding overestimation of resistance levels during outbreaks with resistant bacteria.

This study was not designed to evaluate factors and mechanisms that contributed to the low level of resistant E. coli, Klebsiella spp. and S. aureus. However, there was probably a low entry to the ICUs of epidemic clones of MRSA and E. coli and Klebsiella spp. with the ESBL phenotype as a result of the low prevalence of these strains in Sweden (http://www.rivm.nl/earss/, accessed 2007/06/14). We do not know the main cause of the high imipenem and ciprofloxacin resistance among P. aeruginosa. High consumption of carbapenems and quinolones may be responsible as well as spread of resistant clones. However, phenotypic cluster analysis of recent P. aeruginosa isolates from patients in eight Swedish ICUs showed several different clusters in each ICU (M. Erlandsson, personal communication), indicating a diversity of P. aeruginosa clones. High availability of hand disinfection makes a successful infection control within ICUs possible, although we do not know the level of compliance to hygiene rules in participating ICUs. A relatively conservative antibiotic policy including cefuroxime as the most commonly prescribed drug (7), may also help to minimize resistance rates. Similarly, moderate antibiotic pressure in the community (14, 15) could contribute to a lower carriage of antibiotic-resistant bacteria among Swedish patients admitted to hospitals and ICUs.

The present study indicates that we have a favourable low level of antibiotic resistance among S. aureus and E. coli, but experience from other countries show that this can change rapidly. Still, we believe that there is room for improvement. For example, all local microbiological laboratories should report the current antibiotic resistance patterns in ICU patients on a regular basis. Such reporting will aid updating of empiric treatment guidelines, which is another important area of improvement. There is also a need for better feedback on antibiotic consumption in
addition to a system that alerts clinicians early of the presence of MRSA and other organisms, such as ESBL phenotype of *E. coli* and *Klebsiella* spp. The emergence of outbreaks of ESBL phenotype of *E. coli* or *Klebsiella* spp. in Swedish hospitals illustrated by an ongoing large outbreak in a Swedish University hospital (http://www.akademiska.se, accessed 14/06/2007), are worrying. The threshold for losing control over these outbreaks may be low. Additional significant threats to the current situation include the increased prevalence of multi-drug-resistant bacteria in many European countries (www.rivm.nl/earss/, accessed 14/06/2007) with the risk of import of such strains, and understaffed hospital wards having difficulties in providing isolation precautions and cohort care to carriers.

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