Antibiotic prescription practices, consumption and bacterial resistance in a cross section of Swedish intensive care units

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Background: The purpose of this work was to study usage of antibiotics, its possible determinants, and patterns of bacterial resistance in Swedish intensive care units (ICUs).

Methods: Prospectively collected data on species and antibiotic resistance of clinical isolates and antibiotic consumption specific to each ICU in 1999 were analyzed together with answers to a questionnaire. Antibiotic usage was measured as defined daily doses per 1000 occupied bed days (DDD1000).

Results: Data were obtained for 38 ICUs providing services to a population of approximately 6 million. The median antibiotic consumption was 1257 DDD1000 (range 584–2415) and correlated with the length of stay but not with the illness severity score or the ICU category. Antibiotic consumption was higher in the ICUs lacking bedside devices for hand disinfection (2193 vs. 1214 DDD1000, \( p \leq 0.05 \)). In the ICUs with a specialist in infectious diseases responsible for antibiotic treatment the consumption pattern was different only for use of glycopeptides (58% lower usage than in other ICUs: 26 vs. 11 DDD1000, \( P \leq 0.02 \)). Only 21% of the ICUs had a written guideline on the use of antibiotics, 57% received information on antibiotic usage at least every 3 months and 22% received aggregated resistance data annually. Clinically significant antimicrobial resistance was found among Enterobacter spp. to cephalosporins and among Enterococcus spp. to ampicillin.

Conclusions: Availability of hand disinfection equipment at each bed and a specialist in infectious diseases responsible for antibiotic treatment were factors that correlated with lower antibiotic consumption in Swedish ICUs, whereas patient-related factors were not associated with antibiotic usage.

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one factor that predisposes to infections with resistant bacteria (2,4,5). Frequent and extended use of antibiotics, high staffing and frequent use of invasive procedures make intensive care units (ICUs) a high-risk environment for the selection and spread of antibiotic-resistant bacteria. A recent consensus statement suggested that the emergence of resistance could be better controlled through optimization of prophylactic, empiric and therapeutic antibiotic use (6). This could be accomplished by education about appropriate antibiotic use and by providing data to physicians about the types and prevalence of resistant organisms found in their own institution as part of an on-going surveillance program. Tailoring of antibiotic usage to each ICU by an antibiotic management team led by an intensive care specialist was also suggested recently (7). Indeed, the utility of such a strategy was shown by a recent study in which an antibiotic management program that used local clinician-derived consensus guidelines embedded in computer-assisted decision support programs was applied in a community hospital (8).

While the prevalence of resistant bacterial strains is currently favorable in Swedish ICUs compared with many other European countries (9), we believe that this could change rapidly (10). Monitoring of antibiotic usage and resistance patterns among bacteria are, in addition to prudent use of antibiotics and strict barrier nursing, key elements in the strategy to control resistance to antibiotics. Hence, the main purpose of the present multicenter study was to monitor antibiotic prescription and isolated organisms and their drug susceptibility in individual ICUs and to relate these data to clinical practices associated with the use of antibiotics and infection control measures and patient mix.

Methods

Questionnaires were administered by electronic mail during the year 2000 to all Swedish adult ICUs and departments of infectious diseases. The questions pertained to measures that described the unit and its workload during 1999 (number of beds, number of patients, illness severity scores, length of stay, etc.) and selected infection control practices.

All laboratories of clinical microbiology were contacted and asked to provide data on cultures collected on clinical indications from their matching ICUs during 1999. Only initial bacterial isolates were considered and repeat isolates of the same species from the same patient were excluded. Susceptibility testing was performed at the time of sampling with a disc diffusion method according to the Swedish Reference Group of Antibiotics (SRGA). The zone breakpoints for susceptible, intermediate and resistant strains were defined according to SRGA (11). For the purpose of this work decreased susceptibility to antibiotics was defined as the proportion of isolates with intermediate sensitivity and resistance, i.e. those separated from the normal population of isolates. In addition, hospital pharmacies were contacted and asked to provide data on deliveries of antibiotics to their corresponding ICUs during 1999. Consumption of antibiotics was assessed as the delivery of defined daily doses (DDD) per 1000 occupied bed days in the ICU (DDD1000). Defined daily doses is based on the average adult maintenance dose for the primary indication of the drug and has been established by the WHO as a standardized basis for comparing drug consumption (12).

Significance testing was not carried out to confirm hypotheses postulated a priori but to explore differences and relationships. To this end non-parametric methods (Spearman’s rank correlation, Mann–Whitney, Kruskal–Wallis and Fisher’s tests) were used.

Results

Responses were received from 38 ICUs providing primary services to a population of approximately 6 million. Ten units were located in tertiary care centres (regional ICUs), 20 in county hospitals (county ICUs) and eight were in local hospitals (local ICUs, Table 1). Data regarding patient flow, infection control practices, delivery of antibiotics and microbiology, including resistance patterns, were received from 26 units. Information on bacteriology and susceptibility to antibiotics only were received from five additional ICUs, while patient flow data plus data on the delivery of antibiotics only was received from 31 ICUs.

Among ICU characteristics compared, only the number of admissions and length of stay differed between hospital categories (Table 1). The median number of beds with a strict isolation facility per ICU was two, although three ICUs had no such facility. The mean length of stay in the regional ICUs was more than twofold that in the local ICUs. Eighteen units (47%) collected illness severity scores (APACHE II, n=17, APACHE III, n=1), but only one unit computed a risk of death from the scores. The mean APACHE II scores were slightly higher in the regional ICUs compared with units in the county and local hospitals (Table 1). Only 3/33 (9%) ICUs had formal guidelines relating to the minimum distance between beds in the unit. The actual minimum distance between beds in mul-
Table 1

Intensive care unit characteristics and selected practice parameters.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Local hospital ICU</th>
<th>County hospital ICU</th>
<th>Regional hospital ICU</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual no. of admissions median (range)</td>
<td>2070 (1577–4955)</td>
<td>1746 (591–4950)</td>
<td>1042 (700–1490)</td>
<td>0.03</td>
</tr>
<tr>
<td>No. of beds median (range)</td>
<td>8 (6–11)</td>
<td>8.5 (6–19)</td>
<td>9.5 (6–16)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mean APACHE II scores median (range)</td>
<td>10.4 (10.0–12.8)</td>
<td>12.0 (8.7–16.0)</td>
<td>12.9 (12.7–13.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean length of stay (days) median (range)‡</td>
<td>1.0 (0.3–1.2)</td>
<td>1.4 (0.6–3.2)</td>
<td>2.3 (1.4–4.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Antibiotic consumption (DDD1000) median (range)</td>
<td>1072 (807–1377)</td>
<td>1170 (604–2415)</td>
<td>1541 (584–2247)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Postoperative patients were included in some units, leading to a large number of admissions and short mean lengths of stay.
†P-values refer to comparisons between intensive care unit (ICU) categories.
‡Correlated with total antibiotic usage (P=0.03, see text).
§Negatively correlated with total antibiotic usage (P=0.05, see text). DDD1000, defined daily doses per 1000 occupied bed days. The number of units (n) varies as a result of missing values. Unless otherwise stated the ICU characteristics did not correlate with antibiotic consumption.

Intensive care units with many admissions or short mean lengths of stay had a usage of antibiotics that was significantly lower than the median consumption (P=0.01 and P=0.03, respectively; Table 1). Antibiotic usage in units lacking devices for hand antisepsis at the bedside was on average 1.6-fold higher than the median antibiotic consumption in units with such bedside devices (P=0.05).

Cephalosporins were the most frequently used group of antibiotics (median 26% of the total consumption, Fig. 2), but with considerable variation between the ICUs with regard to usage (173.3–640.4

Fig. 1. Total consumption of antibiotics at individual intensive care units (ICUs). DDD1000, defined daily doses per 1000 occupied bed days. The ICUs are identified by a random two-letter sequence. The horizontal line represents the median value.
DDD\textsubscript{1000}) and the proportion of different generations of cephalosporins (Fig. 3). The use of isoxazolyl penicillins varied considerably (range 24–1271 DDD\textsubscript{1000}) and was associated with a high total consumption of antibiotics (rank correlation between use of isoxalyl penicillins and total use of antibiotics: 0.57, P=0.001). Whereas the consumption of most classes of drugs did not differ between the ICU categories, the median use of carbapenems was lower in the local hospitals compared with county and regional hospitals (58, 110 and 143 DDD/1000 occupied bed days, respectively, P=0.05; Fig. 4). In the ICUs with a specialist in infectious diseases responsible for antibiotic treatment only, the use of glycopeptides differed from that in the other units (median 11 vs. 26 DDD\textsubscript{1000}, P=0.02).

Microbiology and antibiotic resistance
The median number of positive cultures normalized per 1000 occupied bed days was 11.4 (range 2.6–19.2) with no significant difference between the type of unit or association and the presence or absence of an infectious disease specialist. There was no difference in the number of normalized positive cultures and the presence or lack of bedside disinfection devices (P=0.41). We were also unable to establish any relationship between the consumption of hand disinfectant and the number of normalized positive cultures (rank correlation=0.33, P=0.38). All responding units received preliminary information regarding bacterial growth in blood cultures, while 74% of the ICUs received such data also for other specimens. Feedback at the local level on patterns of bacterial resistance to antibiotics was provided at least annually by the microbiology laboratory to 6/28 of the ICUs and at least every 3 months by 17/30 of the ICUs (Table 1).

Among the Enterobacter species (212 isolates), 34% had decreased susceptibility to third generation cephalosporins (cefotaxime or ceftazidime) and 63% of 213 isolates had decreased susceptibility to cefuroxime. Of 710 Enterococcus species isolates from the regional and county ICUs, 25% and 32%, respectively, showed decreased susceptibility to ampicillin, but only 17% of 60 bacterial isolates from the local hospitals (difference between ICU category, P=0.02). Among Pseudomonas aeruginosa, 26% showed decreased susceptibility to imipenem, 11% to ciprofloxacin and 11% to ceftazidime. Decreased susceptibility to isoxazolylpenicillins was found in 70% of 1158 isolates of coagulase-negative staphylococci, but in only...
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not primarily paid by the ICU, and the case in which
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Discussion

This study combines data collected and accumulated
in a prospective manner within hospital pharmacies
and microbiology laboratories with answers to a ques-
tionnaire. Responses were received from a cross-sec-
tion of Swedish adult ICUs covering approximately
70% of the population. There was a relative lack of
data from smaller units in local hospitals (10 out of
33) and tertiary care units in regional hospitals (10 out
of 22). As the data from most of the ICUs of the
county hospitals were collected (18 out of 23) we be-
lieve that the findings mirrored conditions in Swedish
adult general ICUs during 1999 reasonably well.

Barely 50% of the responding ICUs used illness se-
verity scoring systems to define their case-mix. How-
ever, the description of case-mix was probably even
less complete, as admissions to local hospitals typic-
ally include coronary care and postoperative care pa-
tients not routinely scored with any illness severity
scoring system. To partly circumvent the problem of
potentially large differences in case-mix between the
ICUs we aggregated the data per hospital category,
assuming that the case-mix remained fairly similar
within each category.

Nonetheless, it is possible that significant differ-
ences in admission patterns within the same hospital
category contributed to the large difference in con-
sumption of antibiotics. The importance of specific ad-
mission patterns is highlighted by the finding that
cardiothoracic ICUs were among the highest con-
sumers of antibiotics per 1000 occupied bed days.
When analyzed in more detail this resulted from the
large consumption of isoxazolyl penicillins, which are
given routinely postoperatively, and short lengths of
stay.

Most Swedish hospital pharmacies rely on com-
puterized systems to keep track of the delivery of drugs
as part of a reimbursement system within the local
hospital. Pharmaceutical products, including anti-
biotics, are paid for by the local ICU, making disposal
of unused drugs a rare incident. Two potentially more
serious errors might be the occasional local setting in
which antibiotics were administered in the unit but
not primarily paid by the ICU, and the case in which
the ICU was responsible for the cost of antibiotics
used outside the unit. Because these events are rare
we believe that deliveries of antibiotics to the ICU ac-
ceptably mirror the consumption within the unit.
Comparison of consumption of antibiotics between
ICUs was facilitated by the use of DDD corrected for
occupied bed days. This measure depends heavily on
the calculation of occupied bed days, which in this
study was defined as the sum of length of stay (in
hours and minutes) of all admissions during 1999.
While DDD per 1000 occupied bed days (DDD1000) is
a reasonable index of antibiotic use within an ICU (8)
it does not provide any data on the prevalence of pa-
tients receiving the antibiotics.

The specimens collected for cultures were taken at
the discretion of clinicians attending the ICU. It was
beyond the purpose of this work to determine
whether the isolates caused infection or only reflected
colonization of the critically ill. Decreased susceptibil-
ity to antibiotics was defined as the sum of isolates
with intermediate susceptibility or resistance to anti-
biotics. Although this avoids the risk of underestimat-
ing the emergence of isolates with moderately re-
duced sensitivity, it complicates a comparison with
other studies.

The most striking finding of this study of Swedish
adult ICUs was the up to fourfold difference between
the units in antibiotic consumption per occupied bed
day. While we were able to identify some ICU charac-
teristics that were associated with less antibiotic use
there was surprisingly no obvious association be-
tween total antibiotic consumption and ICU category
or case-mix of admissions based on APACHE II
scores. Such a relationship could have been concealed
because we had difficulties in obtaining a satisfactory
picture of the case-mix from individual units. How-
ever, the results are in agreement with the notion that
factors other than patient-related factors determine
the use of antibiotics (6). The total consumption of
antibiotics was high and showed that intensive care
patients were constantly treated with, on average, one
antibiotic or more. Yet, few of the ICUs had formal
guidelines regarding the use of antibiotics, and feed-
back to clinicians from microbiologists regarding pat-
terns of antibiotic resistance was poor.

As selective decontamination of the digestive tract
was not used by any ICU in this study this cannot
account for the large differences. A host of other pos-
sibilities exist, one important such explanation being
differences in case-mix not reflected by APACHE II
scores. Particularly, single-disease tertiary ICUs could
be expected to demonstrate specific patterns of con-
sumption. In agreement with this we noted a rela-
tively high consumption of antibiotics in cardio-tho-
racic ICUs. We believe this to be in part due to the
routine use of perioperative antibiotics, as touched
upon previously in this discussion, and admissions typically having short lengths of stay. The reason for the up to fourfold differences in overall consumption between county hospitals was more difficult to understand.

Relationships with a set of diverse clinical practices and hygiene control measures were sought, but, in contrast to preliminary reports from the European Strategy for Antibiotic Prophylaxis (ESAP, 13), we were unable to establish any association between these selected practice parameters and antibiotic consumption except for a higher consumption in the ICUs without bedside devices for hand disinfection. The ESAP also found considerable heterogeneity in the use of antibiotics in 21 European ICUs of six European countries. In addition, that study observed that the prescription of antibiotics was less when approval was needed from a senior physician/microbiologist and when a list of restricted compounds was defined. Restricted compounds were defined as third and fourth generation cephalosporins, ticarcillin-clavulanate, piperacillin-tazobactam, carbapenems, amikacin, fluoroquinolones and glycopeptides. Increased consumption of these antibiotics were, in the ESAP study, associated with surveillance of colonization in the ICU and with sponsoring of meetings and other PR activities by the pharmaceutical industry, suggesting that factors other than patient-related factors determine the use and choice of antibiotic therapy.

Cephalosporins were the most frequently administered antibiotics in European ICUs in the early 1990s, as shown in the EPIC study (14). This was still true in the present cohort of ICUs with a median of 26% of DDD\textsubscript{1000} being cephalosporins, although the percentage for individual units ranged from 13% to 41%. Such high consumption may be a matter of concern, as evidence accumulates that cephalosporin usage is an important determinant of selection and propagation of multiply resistant micro-organisms (15,16). The proportion between different cephalosporins varied in our study but few units used anything other than second and third generation compounds. Although controversial, recent data suggest that fourth generation cephalosporins are less conducive to the development of bacterial multiresistance (17–19).

The use of carbapenems has increased during the last decade in Swedish ICUs (10). In the present work carbapenems accounted for 9% of total antibiotic consumption measured as DDD, with larger use in county and regional ICUs. An emergence of resistance to carbapenems has been noted among isolates of \textit{Pseudomonas aeruginosa} in association with such increased use (20). We found that 26% of \textit{Pseudomonas aeruginosa} isolates demonstrated intermediate susceptibility or were resistant to imipenem. An additional problem with the increased use of carbapenem is selection of \textit{Stenotrophomonas maltophilia} in ICU patients. While alarming, \textit{P.aeruginosa} and \textit{S. maltophilia} were only found in a small proportion (4% and 2%, respectively) of all positive cultures in the present work.

The consumption of glycopeptides was low in comparison with a recent French study (21). Units depending on a specialist in infectious diseases for the prescription of antibiotics had a generally lower use of glycopeptides, which might be as a result of the awareness among specialists in infectious diseases of the need for restricted glycopeptide usage. Furthermore, the low glycopeptide consumption can be explained by the very low (1%) prevalence of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) in Swedish ICUs, which is also the reason for the comparatively high (15%) isoxazolylpenicillin consumption in the present cohort of ICUs.

Clinically significant resistance to antibiotics was found among \textit{Enterobacter} spp. with decreased sensitivity to second and third generation cephalosporins. This might explain the increased treatment with carbapenems and it suggests that use of second and third generation cephalosporins should be reduced in Swedish ICUs.

Failure to use basic infection control techniques with isolation precautions have been shown repeatedly to be associated with the spread of nosocomial infections within intensive care environments. While most ICUs had one or two single bedrooms, a few units lacked such facilities in agreement with a trend noted during the last decade in Sweden (22). Intensive care unit beds are typically spaced wide apart, as indicated by the long median distances between beds in this study. However, in a couple of ICUs the distances were sometimes most likely too short to allow for efficient barrier nursing. Because hand hygiene remains the most important measure to prevent the transmission of microorganisms (23) a link was sought between the number of bedside devices for hand antisepsis, frequency of clinical infection and consumption of antibiotics. There was a lack of relationship between positive cultures and the availability or consumption of hand disinfectant. Among numerous possibilities this may indicate that the frequency of positive cultures per occupied bed days was a poor surrogate for a clinically significant infection. However, we noted an association between large antibiotic consumption and a lack of devices for hand disinfection at the bedside. This is one of the relationships found in the current work that needs to be assessed carefully in prospectively designed studies.
before a conclusive judgment of a cause-effect relationship can be made.

The heterogeneity in total consumption of antibiotics normalized per occupied bed days suggest that the prescription and use of antibiotics can be improved. Optimization of prophylaxis and the choice and duration of empiric therapy remain critical goals to reduce antibiotic pressure within ICUs. Although this is typically achieved by having regularly updated written guidelines and feedback to all physicians, only 20% of the ICUs in the present study had such formal policies. While there is a lack of studies of optimal antibiotic strategies for preventing the emergence of bacterial resistance, there is consensus that knowledge of trends in usage and costs coupled with insights in local patterns of bacterial resistance are steps toward the prevention and control of emerging bacterial resistance (6). Hence, feedback on the results of this work was provided through the internet to all ICUs and their serving partners. We believe that in establishing such a system to monitor the use of antibiotics and occurrence of bacterial resistance, some of the strategic goals to prevent and control the emergence of antimicrobial-resistant micro-organisms may be achieved. Confirmation of this belief will require continuing efforts in this field with recurrent surveys and monitoring of local prescription practices and bacterial resistance.

References


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