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Microbial resistance: lessons from the EPIC study

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Abstract In 1992, a one day point prevalence study (EPIC) was conducted in European intensive care units (ICUs) to determine the prevalence of nosocomial infection among ICU patients. Of the 10,038 patients included, 45 % were infected and 21 % had a nosocomial ICU-acquired infection. Many of the organisms responsible for these infections were resistant to commonly used antibiotics. For example, 60 % of the *Staphylococcus aureus* isolated were resistant to methicillin and 46 % of *Pseudomonas aeruginosa* were resistant to gentamicin. The incidence of nosocomial infection varied between countries as did the incidence of antibiotic resistance. Mortality rates were higher in countries with higher rates of nosocomial infection and higher again in those countries with higher rates of resistant organisms. Antibiotic resistance is rising and clearly efforts to contain its development and spread are vital. Basic infection control procedures such as hand-washing must be developed and implemented, and antibiotic prescribing needs to be rationalized. The international variations in resistance rates, even within Europe, highlight the importance of being familiar with local resistance patterns when prescribing. The assistance of an infectious diseases specialist can be invaluable in providing a global overview of the local microbial milieu and of antibiotic resistance patterns. Epidemiological studies of this sort can provide useful information which can be used to stimulate debate on the reasons behind regional differences in infection and help in the development of strategies to combat the rising tide of microbial antibiotic resistance.

Introduction

Microbial resistance to antimicrobial agents is becoming more frequent worldwide [1], and multi-resistant organisms are increasingly seen on our intensive care units (ICUs). Methicillin-resistant *Staphylococcus aureus* (MRSA) is now relatively common, and strains of *Staphylococcus* with decreased sensitivity to vancomycin have recently been reported [2, 3, 4]. Enterococci have developed resistance to vancomycin, as well as to many other antibiotics, while Enterobacteriaceae, *Pseudomonas* species and other gram-negative bacilli have become resistant to most frontline antibiotics, including third-generation cephalosporins, monobactams, aminoglycosides and quinolones. Strains of *Pseudomonas* and *Serratia* have been identified which are able to inactivate the carbapenems, and fungal resistance is also rising [5]. In a one-day point prevalence study, data on the incidence and origin of nosocomial infection in 1417 ICUs across 17 Western European countries were collected. This article will discuss the data from this study relevant to microbial resistance and the implications for intensive care antibiotic practice.

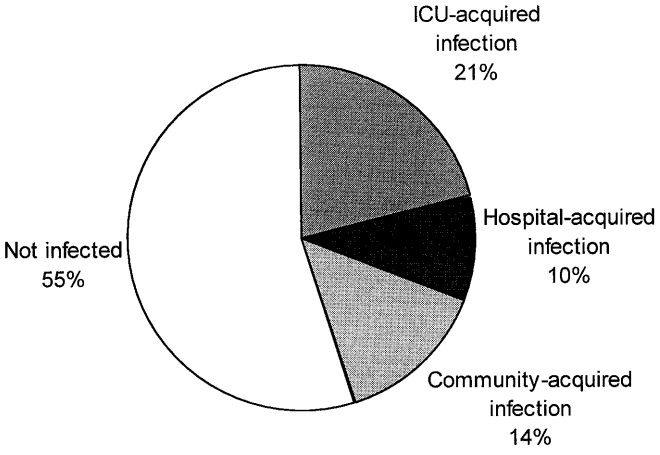

Fig. 1 Numbers of infected patients in the EPIC study and distribution according to origin of infection: community, hospital, or ICU-acquired

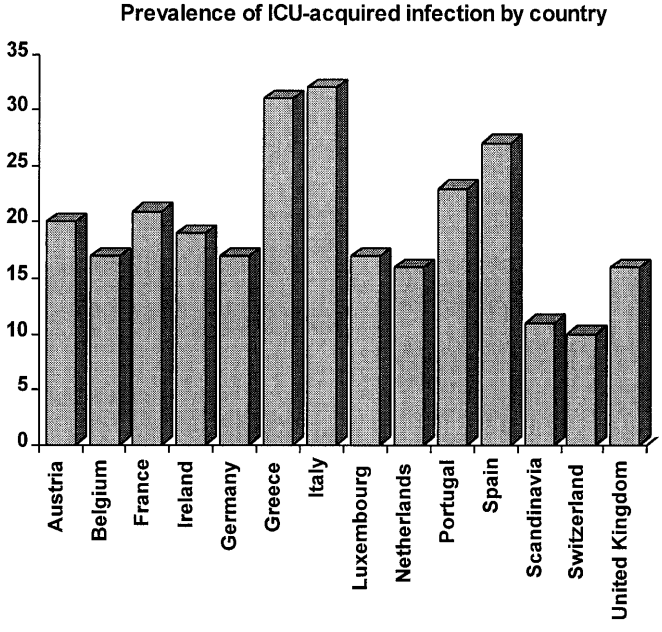

Fig. 2 Prevalence of ICU-acquired infection in the EPIC study by country

EPIC results

In the European Prevalence of Infection (EPIC) study [6] data were collected on all patients over 10 years of age occupying a bed in a participating ICU over a 24-h period from midnight, 28 April to midnight, 29 April 1992. The result was a database of 10,038 completed case report forms. The primary aims of the study were to determine the prevalence of ICU-acquired infection, risk factors associated with infection, and the predominant organisms involved in infection, although a wealth of other information on ICU organization was also obtained [7].

Table 1 Risk factors (logistic regression analysis) for ICU-acquired infection and for death identified in the EPIC study

Risk factors for ICU-acquired infection	Risk factors for death
Pulmonary artery catheterization	Age > 60 years
Central venous access	Organ failure on admission
Stress ulcer prophylaxis	APACHE II score > 30
Urinary catheterization	ICU stay > 20 days
Mechanical ventilation	Pneumonia
Trauma on admission	Clinical sepsis
Length of ICU stay	Laboratory proven bacteremia
	Cancer

On the day of the study, 4,501 patients, i.e., 45% of all ICU patients in participating centers that day, had one or more infections, 21% being ICU-acquired infections (Fig. 1), defined as an infection present on the day of study which had not been clinically apparent at the time of admission to the ICU. The prevalence of nosocomial ICU-acquired infection varied considerably according to country, with the highest rates in Southern European countries (Italy, Greece, Spain and Portugal) and the lowest rates in Switzerland and Scandinavia (Fig. 2). The predominant ICU-acquired infection was pneumonia (47%), followed by other lower respiratory tract infections (18%), urinary tract infection (18%), laboratory confirmed bacteremia (12%) and wound infection (7%). Seven risk factors were identified, by logistic regression analysis, as being associated with the development of ICU-acquired infection (Table 1). Taking the group of patients as a whole, the mortality rate was 17%, varying from 8% in Switzerland to 29% in Greece, being higher in those countries with higher rates of ICU-acquired infection (Fig. 3). Eight factors were identified as being independently associated with an increased risk of mortality by logistic regression analysis (Table 1).

Within the group of patients with ICU-acquired infection, 55% of infections were polymicrobial, and microbiological culture results were available in 85%. *Staph. aureus* was the organism most frequently isolated, in 30% of cultures. Other commonly reported organisms included the Enterobacteriaceae, *Pseudomonas aeruginosa*, coagulase-negative staphylococci, and fungi (Table 2). Details of antimicrobial resistance patterns were reported for *Staph. aureus*, *P. aeruginosa*, and coagulase-negative staphylococci.

Staphylococcus aureus: Five hundred and twenty-eight ICU-acquired infections were associated with *Staph. aureus*, and resistance patterns were reported in 456 of these infections. Sixty percent of the *Staph. aureus* infections were due to MRSA, and in bacteremias where *Staph. aureus* was cultured, 72% were due to

Table 2 Predominant organisms isolated from patients with ICU-acquired infection in the EPIC study

Organism	Percentage of isolates
Staph. aureus	30
P. aeruginosa	29
Coagulase negative staphylococci	19
Fungi	17
E. coli	13

MRSA. The distribution of MRSA varied considerably according to geographical location within Europe, with much higher percentages in Southern European countries [8] (Fig. 4).

Pseudomonas aeruginosa: Five hundred and four ICU-acquired infections were associated with *P. aeruginosa*, and patterns of resistance were reported in 410 cases. Sixty-five percent were resistant to one or more antibiotics: 46% were resistant to gentamicin, 21% to imipenem, 28% to ceftazidine, 26% to ciprofloxacin and 37% to a ureidopenicillin.

Coagulase-negative staphylococci: Three hundred and thirty-five ICU-acquired infections were associated with coagulase-negative staphylococci, and resistance patterns were reported in 279 cases. Seventy-three percent were resistant to one or more antibiotics: 70% were resistant to methicillin, 69% to cefotaxime, 66% to gentamicin, 9% to teicoplanin and 4% to vancomycin.

Implications

Nosocomial infection

Findings from the EPIC study indicate that nosocomial ICU infection is common, and that the mortality rate is higher in countries with higher rates of ICU-acquired infection (Fig. 3). In particular, there is a north/south gradient, with higher rates of ICU-acquired infection and higher mortality rates in southern Europe. The reasons for these differences are most likely related to differences in patient populations, with these southern ICUs having larger numbers of sicker patients, as reflected by higher APACHE II scores.

Patients admitted to the ICU are at high risk of developing nosocomial infection, due to various factors, including the serious nature of their disease process, the high use of invasive therapeutic and diagnostic devices [9], often prolonged periods of mechanical ventilation, long hospital stays and extended therapy with multiple antimicrobials. Not all nosocomial infections will be due to resistant organisms, but the increasing incidence of antibiotic resistance in organisms isolated from patients with ICU-acquired infection makes it imperative that we employ strategies to limit the development of nosocomial infection (Table 3) [10, 11]. Handwashing is the most effective strategy to prevent the development and spread of nosocomial infection, but is perhaps too simple and easily forgotten amid the fast pace of ICU work. In addition, in many European countries, staff wages are high, and the numbers of nurses are therefore kept at minimal levels to restrain costs. With low levels of nursing staff, especially at night, it may simply be impractical to wash hands when, for example, there is an emergency. Limiting costs by reducing nurses may, in fact, increase costs by increasing infections!

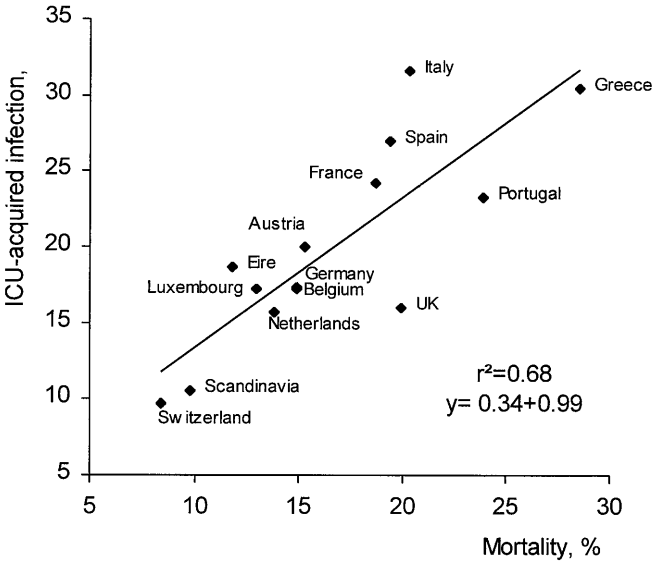

Fig. 3 Correlation of incidence of ICU-acquired infection with mortality (Adapted from [6] with permission)

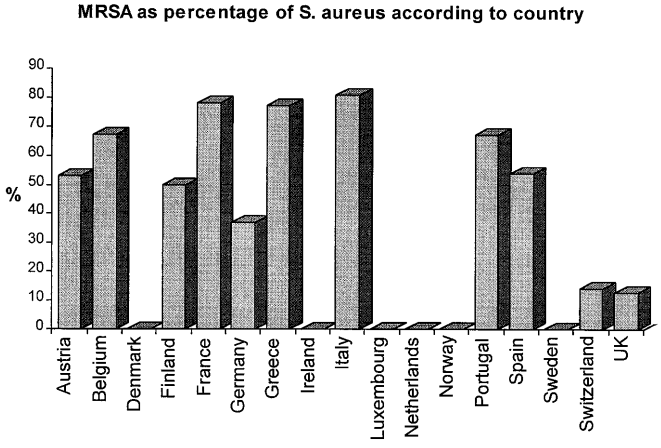

Fig. 4 MRSA as percentage of *Staph. aureus* by country, data from the EPIC study

Table 3 Suggested strategies for limiting development and spread of nosocomial infection

- Hand-washing
- Isolation of patients with resistant organisms
- Selective digestive decontamination
- Early enteral nutrition
- Semi-recumbent positioning of mechanically ventilated patients
- Avoidance of excessive sedation
- Early removal of invasive catheters
- Limited use of nasogastric tubes
- Avoidance of immunosuppressive agents
- Immune-enhancing agents

Table 4 Important principles of antibiotic prescribing

- The presence of fever alone is not a sufficient indication for antibiotics (except in leukopenia)
- Microbiological specimens must be obtained first
- The chosen antibiotic spectrum must be as narrow as possible
- The reasons for antibiotic therapy must be documented
- Treatment must be monitored and re-evaluated
- Antibiotic prophylaxis must be very short

Antimicrobial resistance

Focusing more specifically on antibiotic resistance, the EPIC data reveals that antibiotic resistance occurs frequently among organisms causing infection in ICU patients, a fact supported by other studies within Europe [12, 13, 14, 15, 16, 17, 18, 19] and worldwide [20, 21, 22, 23]. It is clear that the resistance of organisms to antibiotics is increasing [16, 24], and resistance rates are particularly high in the ICU. Archibald et al. [25] reported resistance rates for 13 different antimicrobial/organism combinations and noted significantly higher resistance rates in ICU patients than in other hospital or outpatient groups. Other groups have similarly reported higher resistance rates in ICU patients than in non-ICU patients [16, 21]. Although the increasing incidence of resistance has been clearly documented, the commonly accepted association of these resistant organisms with increased mortality has not been so clearly documented. This may be due, in part, to the fact that ICUs are generally familiar with local resistance patterns and empirically employ alternative antibiotic treatment regimes [26]. However, some studies have suggested higher mortality rates in various groups of patients infected with resistant organisms [27, 28, 29, 30, 31]. In the EPIC study, mortality rates were higher in countries with higher ICU-acquired infection rates (Fig. 3) and higher again in those countries with higher MRSA ICU-acquired infection rates, suggesting that methicillin resistance plays a negative role in survival. Mortality was higher in MRSA infections than in methicillin-sensitive *Staph. aureus* infections (32 % vs 25 %), although this difference was not statistically significant [8].

Antimicrobial prescribing

With the high rates of antibiotic-resistant organisms reported in the EPIC study, and the likely association between resistant infection and poor outcome, these data are clearly worrying in terms of mortality among our ICU patients, and attempts must be made to contain this seemingly rising tide in emergence of resistant organisms. Excessive antibiotic use has been identified as being linked with the development of resistance [32], and the institution of antimicrobial control programs has been reported to increase bacterial antibiotic susceptibility [33,34]. Guidelines on the prevention of antimicrobial resistance have been developed and focus largely on appropriate antibiotic prescribing [35]. In the EPIC study, 62 % of the patients studied were receiving an antibiotic either as therapy or prophylaxis, and 51 % were receiving more than one agent. Antibiotic use is widespread and, indeed, it is often tempting in a sick febrile patient in whom a diagnosis remains elusive to leap in with antibiotics. Clearly, our approach to antibiotic prescribing needs to be rationalized. Table 4 presents some important principles of antibiotic prescribing. Essentially, the diagnosis of infection must be supported by more than suspicion; fever alone is an insufficient indication for antibiotic therapy, other clinical evidence of infection and/or the recognition of other signs of sepsis is necessary. Before commencing antibiotics a full microbiological specimen screen must be taken, and once started, the spectrum of antibiotic cover must be kept as narrow as possible and regularly reviewed and adapted according to results of laboratory culture. The suspected source and origin of the infection, any recent previous antibiotic use, the severity of infection, and available bacteriological information are all important factors to be taken into consideration in the choice of antibiotic for each patient. In addition, the wide variations in antibiotic resistance patterns seen across Europe in the EPIC study [6] highlight the importance of a sound knowledge of local organism ecology and resistance patterns in antibiotic selection. I believe that close collaboration with infectious disease specialists is essential in these matters. Antibiotic prescribing is not a one-to-one patient/doctor issue (as is the prescription of a diuretic or inotrope, for example); rather, by altering the local microbial milieu, it can potentially have widespread effects on other patients, even influencing their chances of recovery. Guidelines must be provided and audits conducted at local and regional level. In our department, infectious disease specialists visit every day to discuss all infectious disease problems with the residents and are available for consultation 24 h a day, 365 days a year. Importantly, the infectious disease specialist is not there to take over patient

antimicrobial management, but rather to provide useful suggestions from a more global, hospital-based viewpoint. Appropriate antibiotic therapy can then be discussed, with the intensivist remaining responsible for the final prescription.

Conclusion

Results from the EPIC study were obtained by questionnaire and must be interpreted with recognition of the limitations that this type of survey can impose, including selection bias due to the voluntary participation of the ICUs [6]. Nevertheless, it is apparent that anti-microbial resistance to antibiotics is common, with as many as 81 % of *Staph. aureus* organisms being resistant to methicillin. Adherence to basic infection prevention strategies and careful antibiotic prescribing are important in limiting the development of nosocomial infection and antibiotic resistance. Incidences of resistant organisms vary greatly between countries and thus an accurate and up-to-date knowledge of local resistance patterns is essential in the choice of antibiotic. Infectious disease specialists can provide an invaluable global overview of current, local antibiotic resistance, and should be routinely involved in discussions related to antibiotic prescribing.

Epidemiological studies, such as EPIC, provide valuable data on the international differences in infection and resistance rates. Such results should encourage and stimulate us to evaluate the reasons behind such differences and, in so doing, to identify methods to limit the development of nosocomial infection and of microbial antibiotic resistance.

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