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Epidemiology of infection in ICUs

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Abstract. Patients admitted to ICUs are at the greatest risk of acquiring nosocomial infections, partly because of their serious underlying disease, but also by exposure to life-saving invasive procedures. Nosocomial infections increase patient morbidity, increase the length of hospital stay and hospital costs, and may increase mortality rates. When serious infections are suspected, treatment must be commenced immediately to increase the likelihood of a satisfactory outcome for the patient. Empirical knowledge, to select appropriate antibiotics, must be used so that the most likely infecting organisms are treated. In the past this has meant that antibiotics with activity against Gram-negative pathogens were most likely to be selected. However, infections where Gram-positive pathogens are responsible (e.g. *Staphylococcus aureus, Staphylococcus epidermidis* and enterococci) are increasingly being found. The European Prevalence of Infection in Intensive Care Study (EPIC), the largest point-prevalence study of infection in ICUs in Western Europe was carried out on 28 April 1992. Data on 10,038 patients in 1417 adult ICU departments from 17 countries was collected and analysed. Of the ICU patients surveyed, 21% had at least one infection acquired in an ICU. The most common infections acquired in an ICU were pneumonia (47%), other infections of the lower respiratory tract (18%), infections of the urinary tract (18%) and infections of the bloodstream (12%). The bacterial isolates were equally divided between Gram-negative and Gram-positive species. The commonly reported bacteria were Enterobacteriaceae (34%), *S. aureus* (30%), *Pseudomonas aeruginosa* (29%), coagulase-negative staphylococci (19%) and enterococci (12%).

Key words: Nosocomial infections – ICUs – Mortality – EPIC – Gram-positive pathogens – Methicillin-resistant *Staphylococcus aureus*

Nosocomial infections represent an important public health problem in the world today [1, 2]. The nationwide rate of nosocomial infection in the USA was estimated to be 5.7 nosocomial infections/100 admissions to acute care hospitals between 1975 and 1976; this is more than the number of hospital admissions for either cancer or accidents, and at least four times greater than the number of admissions for acute myocardial infarction [2]. Prevalence surveys have indicated a variation in the prevalence rates of nosocomial infection from 6 to 17% [3–10]. Infections of the urinary tract, wound and respiratory systems are the commonest types of nosocomial infections [3, 5, 6, 8]. Mortality related to nosocomial infections is significant [2], and the cost of excess hospitalization caused by nosocomial infections in the USA was estimated in 1991 at 2.38 billion dollars/year. In countries where the average duration of hospitalization is longer than the USA, as in many European countries, the risks of acquiring infection are increased. In 1982, it was estimated that decreasing the rate of infection by 10–24% in Germany would result in savings of DM 63–800 million/year [11].

The past few years have seen a rapid growth in antimicrobial resistance, an increase in the number of patients with impaired immunity, a growing emphasis on the use of technology and instrumentation, the recognition of new microorganisms causing infection and an increasing focus on cost control [12]. The costs, morbidity and mortality related to nosocomial infections can only be expected to increase in the future. The prevention and control of nosocomial infections is, therefore, of growing importance.

Staphylococcal infections may, once more, play a part in precipitating the growth in programmes for the prevention and control of nosocomial infections. The evolution of methicillin-resistant *Staphylococcus aureus* has contributed to the resurgence of staphylococcal infections as a major hospital problem [12]. The staphylococcal pandemic in the late 1950s demonstrated the need for an organized effort for the control of infections; it was not until the 1970s, however, that this need was translated into action in the USA, with a dramatic increase in the number of hospitals initiating programmes for the control of infections.

Patients admitted to ICUs have a greater risk of nosocomial infection than other hospitalized patients [7, 13, 14]. Compared with patients in general medical/surgical wards, who have been found to have an overall risk of 6% of acquiring an infection during their hospital stay, critically ill patients in the ICU have been found to have an 18% risk [13]. Nosocomial infections are more common in ICUs because of the severity of the underlying disease, the duration of the stay in hospital, the use of invasive procedures, contaminated life-support equipment,

crowding and the prevalence of multiply resistant microorganisms [15].

The risk of acquiring a nosocomial infection increases with the length of stay in the ICU and with the use of devices [16], and infections are one of the most common causes of death in ICUs [17]. Nosocomial infections vary in incidence and type between different ICUs [15], and knowledge of the patterns of nosocomial infection is of value in the adoption of appropriate policies for the control of infection within an ICU [15]. Furthermore, programmes for the control of infection have been shown to reduce the rate of nosocomial infections in ICUs [17]. Targeted surveillance and the subsequent initiation of appropriate measures for the control of infection in ICUs is, therefore, likely to result in lower morbidity and mortality related to nosocomial infections and to be cost effective.

Computerized surveillance of infection [18] in the ICU at the Royal Hallamshire Hospital, Sheffield, has shown that the source of infection is as follows: respiratory tract 49%; surgical wounds 22%; bloodstream 17%; and urinary tract 12%. The main microbial pathogens are Enterobacteriaceae 35%; *Pseudomonas aeruginosa* 21%; coagulase-negative staphylococci 14%; enterococci 14% and *S. aureus* 6%. The main organisms found in each site of infection are shown in Table 1. Antibiotic susceptibility can also be monitored and the rates of resistance to aminoglycosides are shown in Table 2. It is interesting to note the increasing prevalence of Gram-positive organisms as important pathogens in infections occurring in ICU patients.

Table 1. Comparisons of the nosocomial pathogens, by site, for ICU surveillance at the Royal Hallamshire Hospital

Site and microorganism	Patients in which isolate recovered (%)
Bloodstream	
Coagulase-negative staphylococci	57
Enterobacteriaceae	16
Enterococci	10
Pneumonia	
Pseudomonas aeruginosa	23
Klebsiella spp.	16
Enterococci	11
Staphylococcus aureus	10
Haemophilus influenzae	10
Xanthomonas maltophilia	10
Surgical wound infection	
Pseudomonas aeruginosa	29
Enterococci	21
Staphylococcus aureus	10
Klebsiella spp.	10
Urinary tract infection	
Escherichia coli	25
Enterococci	22
Pseudomonas aeruginosa	21
Klebsiella spp.	14

Table 2. Rates of resistance to aminoglycosides in ICU isolates from the Royal Hallamshire Hospital

Microorganism	Rate of resistance (% microorganisms)
Gram-negative	
Klebsiella spp.	2
Enterobacter spp.	3
Pseudomonas aeruginosa	32
Xanthomonas maltophilia	36
Acinetobacter spp.	77
Gram-positive[a]	
Staphylococcus aureus	0
Coagulase-negative staphylococci	70
Enterococci	90

[a] All Gram-positive isolates were susceptible to vancomycin and teicoplanin

European Prevalence of Infection in Intensive Care (EPIC) study

When infection occurs in an ICU patient it may take up to 72 h for microbiological confirmation of the causative pathogen and for its antibiotic susceptibility to be established. The choice of the most appropriate empirical treatment can therefore be guided by information obtained from surveillance.

Most of the studies of nosocomial infection focusing specifically on ICU to date have been carried out in the USA. European prevalence studies have tended to examine hospital-wide rates of nosocomial infection. On 29 April 1992, a single-day prevalence study of infection in ICUs and 17 countries throughout Europe took place the European Prevalence of Infection in Intensive Care study (EPIC).

This 1-day study of infection in ICUs across Europe was designed to establish the prevalence of nosocomial and other infections in ICUs and to establish the relative importance of risk factors for these infections. In addition, data were collected on the clinical status of the patient on admission (APACHE II scores) and on patient outcome during a 6-week period following the study day. All types of ICU in the 17 countries were eligible to take part in the study, with the exception of paediatric special care baby units and coronary care units.

Data were collected by questionnaire on the presence or absence of infections (according to definitions from the Centers for Disease Control), including nosocomial pneumonia, wound infection, urinary infection and septicaemia, and on the microbiology of these infections. Specific data were collected on the incidence of problem pathogens such as methicillin-resistant *S. aureus* and *P. aeruginosa*. To evaluate the impact of risk factors on the rates of infection, the following data were recorded for each patient: clinical status on admission, presence of iatrogenic risk factors such as intravenous lines, and the use of specific intervention such as selective decontamination of the digestive tract. Basic demographic details were collected on each participating unit.

Data from 1417 participating units were entered onto the study database, together with data for 10,038 patients. Outcome data were available for 9567 (95%) of the patients. Most units were described as mixed medical and surgical units with a median spread size of 6–10 beds/unit. On the day of study, 79% of the beds were occupied. The patient database showed a ratio of

2 men:1 woman, with mean ages of 51 and 61 years, respectively. As anticipated, there was a high level of invasive intervention: 78% of patients had intravenous catheters, 75% had urinary catheters, 64% had central-venous lines and 63% of patients were receiving some form of assisted ventilation.

The level of infection reported on 29 April 1992 was surprisingly high; a total of 45% of patients on these units on the study day had an infection. Infection directly related to admission to the ICU was reported in 21% of cases, infection acquired in the community was reported in 14% and nosocomial infection acquired elsewhere in the hospital was reported in 10%.

The most commonly recorded infections among the 21% of patients with infections acquired in the ICU were pneumonia (47%), other lower respiratory tract infections (18%), urinary tract infections (18%), laboratory-confirmed septicaemia (12%) and wound infection (7%). The most commonly reported bacterial isolates acquired in the ICU infections overall, were *S. aureus* (30%), *P. aeruginosa* (29%), coagulase-negative staphylococci (19%), *Escherichia coli* (13%), enterococci (12%), *Acinetobacter* spp. (9%) and *Klebsiella* spp. (8%) (see Table 3).

Where antibiotic resistance was reported, 60% of *S. aureus* strains were resistant to methicillin. The strains of *P. aeruginosa* showed *in vitro* resistance to gentamicin (65%), ureidopenicillins (38%), ceftazidime (28%), ciprofloxacin (26%) and imipenem (21%).

The EPIC study has again confirmed pneumonia to be the most common infection in ICUs and certainly the most important from a mortality standpoint.

Nosocomial ventilator-associated pneumonia

Widespread use of invasive techniques, such as endotracheal intubation and ventilator-assisted ventilation, while improving the care of critically ill patients, has resulted in new problems of hospital infection, such as ventilator-associated pneumonia (VAP) [19]. Indeed mechanical ventilation itself has been viewed as the major risk factor for nosocomial pneumonia in ICUs [20].

Table 3. Most commonly reported microorganisms in infections acquired in the EPIC study

Microorganism	Patients in which isolate recovered (%)
Staphylococcus aureus[a]	30
Pseudomonas aeruginosa	29
Coagulase-negative staphylococci	19
Candida spp.	17
Escherichia coli	13
Enterococci	12
Acinetobacter spp.	9
Klebsiella spp.	8
Streptococci	7
Enterobacter spp.	7

[a] Where susceptibility was reported, 60% of *Staphylococcus aureus* strains were methicillin resistant

Pneumonia is the most common nosocomial infection in ICUs, accounting for one-third of all infections. It is also the leading cause of death among infections acquired in the ICU [21]. In the review by George [22], 22 epidemiological studies reported infection rates (numbers of cases per 100 patients) of pneumonia in ventilated patients, ranging from 8 to 54 cases per 100 patients, with a median of 27 cases per 100 patients. The ratios were highest in surgical ICUs.

Of the different types of infections acquired in hospital, pneumonia is responsible for the highest mortality [23]. Mortality from nosocomial pneumonia is widely reported to exceed 40% and is assumed to reflect the direct effect of lung infection. There is evidence, however, to suggest that the mortality is more a function of the severity of the underlying disease, than lung infection *per se*. Several other factors are associated with a greater risk of mortality: aerobic Gram-negative bacilli, especially *P. aeruginosa*, as a pathogen; the severity of the underlying disease, especially neoplasia; inappropriate antibiotic therapy; extremes of age; shock; bilateral lung infiltrates; previous antibiotic therapy; and duration of hospitalization before admission to the ICU.

A variety of microorganisms appear to be important causes of VAP. In the USA, the National Nosocomial Infection Surveillance system found that between 1986 and 1989 the most commonly encountered pathogens were Enterobacteriaceae (32%), *P. aeruginosa* (17%) and *S. aureus* (16%) [24]. As with any surveillance study involving VAP, it is not known whether these isolates from bronchial secretions represent the true causal microorganisms involved in VAP. It is known that cultures of tracheal, oropharyngeal secretions and sputum do not reliably identify those pathogens that cause pneumonia [25]. Species that are commonly encountered in respiratory infections acquired in the community, such as *S. pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* are aetiological causes when nosocomial pneumonia occurs soon after admission to the ICU.

The main reason that pneumonia develops in mechanically ventilated patients is aspiration of the microorganisms. The most likely route is along the outside of the endotracheal tube, rather than through the lumen [26]. Intubation predisposes to aspiration of the microorganisms by breaking the natural barrier between the trachea and the oropharynx, severely impairing effective clearance of oral secretions, and damaging the respiratory mucosa by trauma and lack of humidity. Both the stomach and oropharynx are considered to be likely reservoirs for potential pathogens that can be aspirated. Factors found to increase the risk of VAP significantly include chronic pulmonary disease, gastric aspiration, re-intubation, length of time of mechanical ventilation, extremes of age, H_2-antagonist therapy and concurrent elevated gastric pH.

Preventative measures for VAP should aim at reducing the potential inoculum of microorganisms. Ventilator circuits should be changed every 2 days, together with the instigation of scrupulous handwashing techniques, use of aseptic techniques in manipulations of the respiratory tract, adequate disinfection and maintenance of respira-

tory equipment, and preservation of gastric acidity. It is important that procedures to control infection are in place and that compliance is carefully monitored.

Although much progress has been made recently with the diagnosis of VAP, there is still no general agreement about the optimal procedures. Many clinicians diagnose VAP using clinical criteria, which are unfortunately not very specific. In addition, the upper respiratory tract of hospitalized patients is rapidly colonized by potential pathogenic Gram-negative bacteria; therefore, cultures of tracheal secretions cannot be analysed accurately. Two diagnostic techniques, protected specimen brushing and bronchoalveolar lavage, have shown promising results, but their accuracy in some groups of patients (e.g. those with adult respiratory distress syndrome, chronic obstructive pulmonary disease or those receiving antibiotics at the time of sampling) has yet to be proven.

Although the development of broad-spectrum antibiotics may have improved the prognosis of VAP, prevention is more important.

One approach to prevent VAP has been the use of selective decontamination of the digestive tract. However, the use of this approach, by means of non-absorbable antibiotics, remains controversial. There is evidence that the regimen reduces the incidence of secondary infection, but no convincing reduction in morbidity or mortality has been shown, and the costs and effect on antimicrobial resistance patterns need further study. As shown by EPIC, the most common site of infection is the lower respiratory tract. Most of these infections are thought to be endogenous and secondary to the aspiration of pharyngeal secretions, which have become colonized by resistant organisms from the hospital environment.

Selective decontamination of the digestive tract, by which the anaerobic bacteria are preserved and potentially pathogenic aerobic Gram-negative bacteria are eliminated from the gastrointestinal tract, with non-absorbable enterally administered antibiotics, has been studied widely. However, because of flaws in the design, including the use of historical control groups and small numbers of patients for analysis, the results are inconclusive [27].

Nevertheless, selective decontamination of the digestive tract has been adopted by some units. Although the procedure reduces secondary infections, especially of the respiratory tract, there is no convincing evidence of any reduction in morbidity or mortality, or in the overall cost of intensive care [28, 29].

Table 4. The use of intravascular catheters in the ICU at the Royal Hallamshire Hospital[a]

Type of device	Number used annually
Peripheral venous catheter	1454
Peripheral arterial catheter	1370
Central-venous catheter (single lumen)	232
Central-venous catheter (triple lumen)	272
Swan Ganz catheter	270

[a] Six beds in the ICU: a total of 592 patients over 12 months

Device-related septicaemia

In ICUs, the use of intravascular catheters is common (Table 4). Approximately 50% of intravascular catheters are central and 50% are peripheral. Local complications (e.g. phlebitis) occur significantly more often with peripheral than with central catheters. In contrast, fever and septicaemia are significantly more associated with central than with peripheral lines.

Almost any organism can be isolated from an infected line, but it is the Gram-positive bacteria that predominate. *S. epidermidis* is the most common isolate, followed by *S. aureus* and *P. aeruginosa*. No significant risk factors are associated with peripheral catheters. In contrast, three factors, the duration of catheterization, the use of semipermeable transparent dressings and a femoral insertion site, are found to be independently associated with positive cultures of central catheters by multivariate analysis.

Intravenous catheters, like all foreign plastic or metal devices, provide a surface on which bacteria can multiply, at least partially shielded from the humoral and cellular mechanisms that usually clear microorganisms from body tissue [30]. Much work has concentrated on the ability of *S. epidermidis* to produce "slime" and its effects on the defence mechanisms of the host. Slime is not a true capsule; it appears to be loosely bound to the cell surface and is easily removed by washing with water.

Enhancement of the production of slime *in vitro* can be achieved by supplementing the culture media with casamino acids and various sugars. Is slime involved with the adherence of staphylococci to the catheter? Ultrastructural studies show that slime only appears 12 h after exposure of the catheter segments to *S. epidermidis*. The kinetics and mechanics of adherence of *S. epidermidis* probably involves at least two processes. The first is an initial non-specific binding, related to surface charge or hydrophobic interactions or both, between the cell surface and the surface of the plastic devices. The ability of microorganisms to produce slime at this stage is not significant. The second is colonization, as expressed as a function of the production of slime. The slime surrounds the microcolonies of staphylococci and cements them firmly to the surface of the catheter. The production of slime has been suggested as a marker of pathogenicity of *S. epidermidis* and catheter-associated infections.

It is apparent that the prevention of line-associated infections is preferable to cure. Perhaps regular, specialized training of medical personnel in the correct techniques for the insertion of catheters should be widely adopted. Properties of the materials and methods used in the production of cannulas also need to be developed. Ideally, the intravenous lines should be inert and have smooth surfaces from which no substances can leach out, so that bacterial attachment and thrombus formation are prevented. Incorporation of antibacterial agents in catheters is another approach, but problems of stability and leaching, together with the possibility of the emergence of resistant organisms, remains. Currently, however, it is apparent that awareness of line-associated infections, with the adoption of appropriate preventative measures by col-

laboration between clinicians and microbiologists, is one of the most important control factors.

One of the most appropriate preventative measures would appear to be disinfection of the sites for insertion of catheters with a chemical antiseptic, such as 70% alcohol, 10% povidone-iodine or 2–4% aqueous chlorhexidine. Alcohol solutions, particularly 60–70% *n*-propanol or isopropanol are generally more effective than antiseptic detergents and soaps. Isopropanol is especially effective for the immediate reduction of the number of skin bacteria. Frequent handwashing by medical and nursing staff with chemical antiseptics is mandatory.

The role of prophylactic antibiotics (not only for glycopeptides) remains uncertain. At present it seems impossible to recommend prophylactic antibiotics as a routine approach for the prevention of vascular catheter-related sepsis.

Conclusions

Colonization with pathogenic microorganisms can best be prevented by emphasizing good standard microbiological practice. Hand hygiene is of prime importance, but unfortunately medical staff remain refractory to change. Only by the monitoring of patients with regular and appropriate specimens for routine examination and culture from potential sites of infection, together with avoiding the unnecessary use of broad-spectrum antibiotics where there are no clinical signs of sepsis, will the incidence of infection in ICUs decline.

Studies on the rates of infection in ICUs [31] have shown that ICU care patients:

- Are the sickest patients in the hospital.
- Are the oldest and the youngest patients in the hospital.
- Are subjected to the most invasive support and monitoring equipment.
- Reside in the most crowded locations in the hospital environment.
- Are given more antibiotic therapy than any other group of patients.
- Often require a long hospital stay.

These factors contribute to the significantly increased risk for ICU patients of developing a nosocomial infection, especially pneumonia, and to the very high mortality due to infection.

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