Nosocomial infections in the intensive care unit

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Abstract
Nosocomial infection in the intensive care unit (ICU) is associated with increased mortality, morbidity and length of stay. It is defined as infection that begins 48 hours after admission to hospital. The commonest types are ventilator-associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), urinary catheter-related infection and surgical site infection. The common pathogens include Staphylococcus aureus, Pseudomonas aeruginosa, Candida, Escherichia coli and Klebsiella species. Antimicrobial resistance is increasing and has emerged from selective pressure from antibiotic use and transmission via health workers. Prevention of infection is fundamental and can be achieved through good antimicrobial use and infection control, including hand hygiene. Grouped, easy-to-follow best practice activities called ‘care bundles’ have been developed to prevent VAP and CLABSI. Microbiological cultures are central to rapid and accurate diagnosis, which improves outcomes and reduces resistance. The principles of treatment include early antimicrobial therapy (after appropriate specimens are taken) targeted to the local microbes, then de-escalation according to culture and susceptibility results. This article summarizes the pathogenesis, risk factors, microbiology, diagnosis, prevention and treatment of VAP, CLABSI and nosocomial urinary tract infection in the adult ICU.

Keywords Catheter-related infections; cross-infection; intensive care; nosocomial infections; urinary tract infections; ventilator-associated pneumonia

Introduction
Nosocomial infection (defined as onset more than 48 hours after hospital admission) in the intensive care unit (ICU) is associated with increased mortality, morbidity and length of stay. Prevalence rates of infection acquired in ICUs vary from 9 to 37% when assessed in Europe and the USA. Case fatality is high, with crude mortality rates up to 50% for bacteraemia. Timely diagnosis, appropriate management and prevention are essential to improve patient outcomes and reduce antimicrobial resistance. The commonest types are ventilator-associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), urinary catheter-related infection and surgical site infection. Other types of nosocomial infection are also important, such as those in immunocompromised hosts and neonates, but beyond the scope of this article.

Microbiology and resistance
Colonization of critically ill patients with nosocomial organisms usually occurs after 48–72 hours of admission; the most important pathogens are displayed in Table 1. The spectrum of nosocomial microorganisms comprises different ones from those originating from the community, with higher rates of resistant organisms. Antimicrobial resistance emerges in ICU because of:
- evolution of resistance in existing bacteria, through selective pressure from antibiotic use
- transmission (usually nosocomial) especially through frequent contact with healthcare workers or via procedures.

Many studies have previously shown increasing incidence of resistant bacteria in ICUs. These include: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Entero-coccus (VRE) and multi-resistant Gram-negatives. All these pathogens are associated with poor outcomes. There is a longer time to receipt of effective therapy; and the newer agents used for treatment often have inferior efficacy, poor pharmacokinetics and increased toxicity (e.g. vancomycin, linezolid, amikacin, colistin). More recently, studies describe success in controlling some types of resistant organisms (most notably reductions in MRSA, particularly attributed to better hand hygiene practices), but with little impact on Gram-negative and fungal resistance.

The emergence of resistant organisms tends to add to the total burden of infections, rather than substituting for the more sensitive organisms previously present. For example, as MRSA becomes endemic in a unit, the total number of staphylococcal infections tends to increase; in contrast in units where MRSA is reduced, the total number of staphylococcal infections tends to come down.

Diagnosis of nosocomial infection
Rapid and accurate diagnosis of nosocomial infection both improves patient outcomes and decreases selection pressure for resistance. It ‘streamlines’ patients onto the most effective treatments allowing rapid cessation of unnecessary antibiotics and minimizing unnecessary side effects. Correct timing is vital.
Common ICU nosocomial pathogens (EPIC II study)²

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Prevalence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>20%</td>
<td>Includes MRSA (10%)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Enterococcus</td>
<td>11%</td>
<td>Includes VRE (4%)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Important Gram-negative resistance mechanisms include:

- Extended-spectrum β-lactamases (ESBLs) 2%: plasmid-encoded genes that confer resistance to penicillins and extended-spectrum cephalosporins. Carbapenems are the treatment of choice.
- AmpC-type β-lactamases: chromosomal or plasmid genes that are similar to ESBLs.
- Metallo-β-lactamases (MBLs): confer resistance to carbapenemases.
- New Delhi metallo-β-lactamases (NDM-1): a recently discovered plasmid-mediated mechanism. May be susceptible to polymixins and tigecycline.

ICU, intensive care unit; MRSA, meticillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant enterococci.

Table 1

with all microbiologic tests. Tests rapidly lose sensitivity once new antibiotics are introduced.

The single most useful microbiologic test in ICU is a correctly performed blood culture. Our unit’s simple protocol is shown in Box 1.

General prevention measures

Nosocomial infections are reduced by good antibiotic use (to maximize cure rates and reduce of selection pressure for resistance) and strict infection control.

Establishing active ongoing liaison between the ICU, infectious diseases (or clinical microbiology) department and pharmacy is essential. This multidisciplinary approach is important to develop local guidelines (preferably guided by local microbiology data), provide day-to-day advice, oversee control measures for broad spectrum antibiotics, and monitor usage and report back to the ICU staff in a useful manner. Elements of good antibiotic use in the ICU are given in Box 2. The role of combination antibiotics in preventing resistance is controversial. However, it is common practice to use combination empiric therapy for sepsis for reasons of coverage, de-escalating to narrower cover once culture results are known or the patient improves. ‘Cycling’ antibiotic use is poorly studied, and cannot be recommended.

Infection control minimizes cross-transmission and prevents colonizing bacteria from causing infection. One of the key elements in infection prevention over the past decade has been hand hygiene. It is estimated that over 30% of healthcare-associated infections are preventable by hand hygiene. Hand hygiene prevents cross-transmission of pathogens by hands of healthcare workers between patients. Multiple studies have shown a reduction in healthcare-associated infection rates, specifically reductions in MRSA and even elimination in some centres. The WHO has recommended ‘Five Moments for Hand Hygiene’ in healthcare settings both resource rich and poor.¹ Alcohol-based hand-rubs should be used before touching a patient, before a procedure, after body fluid exposure, after touching a patient and after touching patient surroundings. Other aspects of infection control include surveillance for, and isolation of, patients with multi-resistant organisms.

Recent years have seen the widespread promotion of infection control ‘care bundles’. These are groupings of ‘best practices’ that when applied together appear to result in greater improvement in outcomes. This is based on the philosophy that the ‘total may be greater than the sum of the parts’. They have the virtues of being simple, logical (mostly) and easily evaluable (the elements are dichotomous, so compliance can be measured as a simple ‘yes/no’). Not all possible proven therapies are included in the bundle, as factors such as ease of implementation, adherence and cost are considered. Examples of care bundles are given in Box 3.

Specific conditions

Ventilator-associated pneumonia (VAP)

Hospital-acquired pneumonia (HAP) (i.e. pneumonia that begins 48 hours or more after admission) is the leading cause of hospital-acquired infection leading to mortality.² Ventilator-associated pneumonia (VAP) is adequate for most cases of ventilator-associated pneumonia. Using shorter duration of antibiotics overall, e.g. 5–7 days is adequate for most cases of ventilator-associated pneumonia. Appropriate dosing will both maximize cure rates and minimize selection of resistance. Unfortunately both under- and over-dosing are common in the ICU setting.
pneumonia (VAP) is a subset of HAP, occurring 48 hours or more after endotracheal intubation. Mechanical ventilation increases the risk of pneumonia by 6–20 times. It is associated with mortality rates of up to 50%. Some authors also describe ventilator-associated tracheobronchitis (VAT) as a precursor condition, differentiated from VAP by the absence of chest X-ray infiltrates. It is unclear if VAT requires treatment, with studies showing it increases ventilation and ICU stay, but not mortality.

The pathogenesis is thought to involve micro-aspiration of oropharyngeal microorganisms, which enter into the lower respiratory tract via leakage around the endotracheal tube cuff or directly through the tube. Aspiration of gastrointestinal microorganisms contributes to a lesser extent. Microbial virulence factors and host defense factors then determine if pneumonia occurs.

Risk factors: the most significant risk factors for VAP include age over 70 years, chronic lung disease, depressed consciousness and aspiration. The key modifiable factors increasing risk for VAP are previous antibiotic exposure, use of paralytic agents, reintubation or prolonged intubation, frequent ventilator circuit changes, presence of a nasogastric tube or intra-cranial pressure monitor. The effect of anti-acid therapy is controversial but this is directly related to the tube. Aspiration of gastrointestinal microorganisms contributes to a lesser extent. Microbial virulence factors and host defence factors then determine if pneumonia occurs.

Microbiology: a wide spectrum of bacteria can cause VAP. Organisms include aerobic Gram-negatives (Escherichia coli, Klebsiella, Enterobacter etc.), Gram-positive cocci (Streptococcus, Enterococcus etc), and oropharyngeal flora; some of these may be multi-resistant. Data from a large American study showed the major pathogens to be methicillin-resistant Staphylococcus aureus (14.8%), Pseudomonas aeruginosa (14.3%), and other Staphylococcus species (8.8%). However the local epidemiology is important. High rates of MRSA are not seen in all countries, for example, and rates may differ markedly between different institutions even in the same city. Viruses and fungi are rarely pathogenic in immunocompetent hosts.

Diagnosis: the optimal diagnostic algorithm for VAP remains unclear. Clinical plus radiological features only have moderate sensitivity (69%) and specificity (75%), resulting in misdiagnosis and overuse of antibiotics. Positive microbiological sampling alone cannot differentiate between colonization, VAT or VAP; however negative cultures from good-quality specimens (before receipt of antibiotics) reasonably excludes VAP. A combination of clinical, microbiological and radiological criteria is required.

Quantitative culture of good-quality bronchoscopy specimens yields the most reliable microbiological result, but has variable application within units due to concerns around cost, logistics and side effects. Less invasive strategies to improve the microbiologic diagnosis include quantitative culture of endotracheal aspirate, blind bronchial sampling or mini BAL. To some extent the best specimen will depend on the expertise and culture within an individual unit. The most important factor is that whatever specimen is preferred, the specimen should be collected before starting or changing antibiotics. More reliable microbiology results translate into improved outcomes in a number of studies, with less antibiotic use (variably showing both fewer patients starting antibiotics, and those on them stopping earlier), less development of resistance, better patient outcomes and increased clinician confidence.

Management: the principles of treating VAP include early antimicrobial therapy (but after appropriate specimens are taken) guided by the local microbiology, then de-escalation according to culture and susceptibility results. In many units this will result in empiric combination therapy to cover multi-resistant organisms (MROs). Aerosolized agents have not been proven for routine use, though may be tried in MROs where options are limited. A total duration of 5–7 days of effective therapy is adequate for most pathogens, though most physicians would treat longer for Pseudomonas or true staphylococcal pneumonia.

Prevention: strategies to prevent VAP include reducing need for ventilation, reducing colonization and reducing aspiration. Non-invasive methods of ventilation are associated with reduced rates of VAP in patients with acute respiratory failure.

Methods to reduce aspiration include avoidance of acid-blocking medications, semi-recumbent patient positioning, subglottic drainage techniques, and silver-coated endotracheal tubes. American guidelines from 2008 have in-depth recommendations but identify avoidance of acid-suppressants, selective decontamination of the digestive tract (SDD) and antiseptic impregnated endotracheal tubes as unresolved issues. SDD remains a contentious area. It involves the application of topical antimicrobials to the oropharynx and/or nasogastric tube, with or without systemic antibiotics. Two meta-analyses have showed it reduces the rate of VAP and reduces mortality in the subgroup treated with systemic agents. However, it is not accepted widely into practice, particularly in North America, due in part to concerns of selection of antimicrobial resistance. It is probably most effective where VAP rates are high but background resistance rates low. Topical antiseptics along with good oral hygiene may be a more acceptable option, but further studies are needed in the ICU setting.

CLABSI
Intravascular catheter-related infections are a major cause of morbidity and mortality in the ICU. A meta-analysis showed...
a case fatality rate of 19% for catheter-related bloodstream infections. We will focus on central line-associated bloodstream infection or CLABSI.

**Risk factors:** host predisposing factors include immunosuppression, burns, malnutrition, use of total parenteral nutrition and extremes of age; however these are not modifiable. The risk of infection increases after day 3. Higher rates of infection in adults are seen with femoral vein insertion sites, then jugular and the least with subclavian.

**Microbiology:** the pathogenesis of infection involves skin flora colonizing the device. The pathogens involved are Staphylococci (coagulase-negative and *Staphylococcus aureus*; 50%), Gram-negative bacilli (30%), enterococci (10%) and *Candida* species (10%). *Staphylococcus aureus* has a significantly higher attributable mortality rate than the other pathogens. Host factors play a role: for example, Gram-negatives predominate in burns patients.

**Diagnosis:** this involves establishing bloodstream infection and showing that the source is the catheter. Paired blood cultures can be obtained from a peripheral vein and via the catheter (bearing in mind that false-positives (i.e. contaminants) are more common from line cultures). If the same volume of blood is drawn at exactly the same time, a delay of 2 hours or more from the central sample becoming positive to the peripheral sample becoming positive strongly points to a central line-related infection. This is referred to as ‘differential time to positivity’ which indicates that the blood from the catheter lumen has a far greater concentration of organisms in it than peripheral blood. Culture of a catheter tip is only useful if the catheter is thought to be infected. There is little evidence for drawing cultures from every lumen of a central line.

**Management:** if CLABSI is suspected, the catheter should be removed, cultures taken (peripheral, tip of central venous catheter) and antimicrobial therapy should be initiated. Management is guided by the identification of the causative organism: *Staphylococcus aureus* bacteraemia (SAB) should be treated for at least 14 days, Coagulase negative *Staphylococcus* for 5–7 days, Gram negatives for 10–14 days, and *Candida* for 14 days. Echocardiography is absolutely indicated in SAB. Most centres have rates of MRSA high enough to empirically include cover for this pathogen until culture results are available.

**Prevention:** simple practices to modify risk factors can eliminate most CLABSI. Insertion should be performed using strict aseptic technique by an appropriately experienced person. Local protocols should reinforce the following evidence-based activities: hand washing/strict aseptic technique, full barrier precautions, 2% chlorhexidine for skin disinfection, antiseptic impregnated sponge dressings. Vigilant catheter care is essential, in particular antiseptic wipes on ports before access. All catheter insertion sites should be assessed daily for infection. Removal of unnecessary catheters is vital, but often overlooked. If inserted under emergency conditions they should be removed/replaced within 48 hours. Guide-wire exchange techniques should not be used, as higher rates of bacteraemia result. Peripherally inserted central catheters are routinely left in place for months, but reliable data regarding infection risk of these devices in ICU are lacking. Meta-analyses have shown lower rates of CLASBI with antimicrobial coated central venous catheters and these may be of benefit in units with high rates of CLABSI, or selected patients at high risk. Antiseptic-coated central venous catheters appear less effective, but have fewer concerns around selection pressure for resistance.

**Nosocomial urinary tract infections**

Catheter-associated urinary tract infection (CA-UTI) refers to infection occurring in a person whose urinary tract is currently catheterized (or has been catheterized within the previous 48 hours). Significant bacteriuria may also occur in a patient without symptoms or signs attributable to the urinary tract. This is termed catheter-associated asymptomatic bacteriuria (CA-ASB). Encouragingly, a national US survey showed that rates of CA-UTI and CA-ASB have declined from 1990 to 2007.

Pathogens usually ascend from the urethral meatus on the external surface of the tube. However, one-third ascend intraluminally (e.g. from a contaminated bag).

**Microbiology:** in addition to the community-acquired pathogens (Gram-negatives, enterococci), the bacteria causing CA-UTI in the ICU include *Staphylococcus* and *Pseudomonas*. The presence of *Candida* species is a common finding which normally represents colonization in patients who have received broad-spectrum antibiotics even in immunocompromised hosts. Rarely, it reflects the presence of candidaemia (1.3% in one study).

**Risk factors:** include prolonged catheterization and bacterial colonization of the drainage bag.

**Diagnosis:** it can be difficult to distinguish true pathogens from colonizing organisms. Urine cultures should be obtained prior to antibiotic administration, and not from the drainage bag. A catheter change prior to sampling avoids culturing colonizers.

**Management:** it is essential that a urine culture is obtained prior to the initiation of treatment. Treatment duration for patients who respond promptly to antibiotics is 7 days and 10–14 days for a delayed response.7 Asymptomatic candiduria usually resolves with catheter change.

**Prevention:** the principles of prevention are avoiding catheterization where possible, aseptic technique and catheter care, early removal and considering intermittent catheterization. Antibiotic impregnated catheters are proven to be effective and likely to be cost effective. It is unclear if they select for resistant organisms. There is no evidence to support the use of prophylactic antibiotics during catheter insertion and removal.

**REFERENCES**


