Nosocomial infections in the ICU

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Abstract

Nosocomial infections are a major cause of avoidable morbidity, mortality and extended length of stay in ICU. Prevention of these infections is key. Continual surveillance, audit and hand hygiene are therefore vital. The recent introduction of 'care bundles' grouping best practices for care of invasive devices have proven highly successful for reducing the rates of nosocomial infection in the ICU. Despite these strategies patients in the ICU are still twice as likely to contract a nosocomial infection compared to the general hospital population. Furthermore, the microbes involved tend to be more difficult to eradicate due to increasing microbial resistance. The most common nosocomial infections contracted in critical care are ventilator-associated pneumonia, central line-associated blood stream infection and urinary catheter-related urinary tract infection. Timely recognition and management of these conditions is key to providing best care within the ICU. The focus of therapy should always be targeted to specific microbes with information guided by initial cultures and sensitivities. This, combined with regular liaison with local microbiology colleagues, will ensure the best treatment with the least risk of causing selective pressures and further multi drug resistance.

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

Royal College of Anaesthetists CPD Matrix: 1A01, 1E01, 2C03, 2C07

Learning objectives

After reading this article, you should be able to:
- outline the burden of nosocomial infection in the ICU
- describe the issues relating to antimicrobial resistance and common clinical actions that can lead to this
- discuss the strategies, including care bundles, to prevent nosocomial infections in ICU

Introduction

Nosocomial infections include all infections acquired between 48 hours after hospital admission and 3 days of hospital discharge. Hospital-wide, they affect one in ten patients and result in a significant cost (around £1 billion) to the National Health Service. The European Prevalence of Infection in Intensive Care (EPIC) Study[1] demonstrated nosocomial infection prevalence in ICU to be significantly higher at around 20.6%. The majority of these are associated with the use of invasive devices (endotracheal tubes, central venous catheters and urinary catheters). Up to a third of these may be considered preventable. Each infection is associated with increased patient mortality, morbidity and length of ICU stay. Furthermore, the burden of antimicrobial resistance in ICU is high, and increasing. This is likely due to the severity of each patient's clinical condition, frequent antibiotic use, and variation in infection control practices.

The most common infection types are ventilator-associated pneumonia (VAP), central line-associated blood stream infection (CLABSI), urinary catheter-related infection and surgical site infection. Continual mindfulness and timely diagnosis of these conditions with appropriate management improves patient outcomes. The most successful intervention, however, is prevention of infection transmission. This includes general measures such as fastidious hand washing, antimicrobial stewardship and the use of best practice 'care bundles'.

The most frequently isolated organisms found in nosocomial infections in ICU are shown in Table 1.

Risk factors

There is a direct positive correlation between average length of ICU stay and rates of nosocomial infection.[2] Each invasive procedure performed poses its own risk of infection. Multiple studies have shown increased rates of nosocomial infection with central venous catheterization, mechanical ventilation, tracheostomy, and urinary catheterization.[3] Table 2 shows all risk factors thought to lead to increased likelihood of nosocomial infection in ICU.

Microbiology and resistance

Critically ill patients display a different spectrum of colonization to that of the rest of the hospital population. Nosocomial growth occurs within 48–72 hours of admission, and displays far higher rates of drug-resistant organisms. Resistance occurs due to selective pressures from regular antibiotic use, causing *evolution* of existing bacteria. This problem is then compounded by *nosocomial transmission* of these resistant species. The most common mode of transmission is unfortunately via healthcare workers and invasive procedures.

Common resistant bacteria found in the ICU are:
- methycillin-resistant *Staphylococcus aureus* (MRSA)
- vancomycin-resistant enterococci (VRE)
- multidrug-resistant (MDR) Gram negatives (see Box 1).

There are several important negative clinical consequences of acquiring a resistant organism. Drug-resistant organisms notoriously take longer to be recognized and cultured, resulting in a delay to receipt of effective therapy. The therapeutic agents used (e.g. vancomycin, linezolid, daptomycin) are more often

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Percentages of the most frequently isolated micro-organisms in nosocomial infections in the ICU (ECDC study)

Micro-organism	Ventilator-associated pneumonia (%)	Bloodstream infection (%)	Urinary tract infection (%)
Pseudomonas aeruginosa	27.5	4.6	10.6
Staphylococcus aureus	12.5	18.5	1.6
Klebsiella spp.	10	10.8	6.1
Escherichia coli	15	9.2	18.2
Enterobacter spp.	15	6.2	5.7
Candida spp.	2.5	12.3	15.3
Serratia spp.	5	0	
Stenotrophomonas multophilia	12.5	0	
Haemophilus spp.	0	0	
Enterococcus spp.	0	13.8	13.8
Coagulase-negative staphylococci	0	20	3.1
Acinebacter spp.	0	4.6	

1. European Centre for Disease Prevention and Control. Annual Epidemiological Report 2016 — Healthcare-associated infections acquired in intensive care units.
2. NNIS System. National Nosocomial Infections Surveillance System January 1989—June 1998. A report from the NNIS System. Am J Infect Control 1999 Dec; 27(6): 520-32.

(UTI Data from National Nosocomial Infections Surveillance System January 1989—June 1998.)

Table 1

Factors leading to increased risk of nosocomial infection

Patient factors		Healthcare factors	
Chronic	Acute	Invasive procedures	Treatment
Advanced age (>70)	Surgery	Endotracheal or nasal intubation	Blood transfusion
Malnutrition	Trauma	Central venous catheter insertion	Recent antimicrobial therapy
Alcoholism	Burns	Extracorporeal renal support	Immunosuppressive treatments
Heavy smoking		Surgical drains	Stress-ulcer prophylaxis
Chronic lung disease		Nasogastric tube	Recumbent position
Diabetes		Tracheostomy	Parenteral nutrition
		Urinary catheter	Length of ICU stay

Table 2

Important mechanisms of Gram-negative resistance

- **Extended-spectrum beta-lactamases (ESBLs):** plasmid-encoded genes that confer resistance to penicillins and extended-spectrum cephalosporins.
- **AmpC-type beta-lactamases:** Chromosomal or plasmid genes that are similar to ESBLs.
- **Metallo-beta-lactamases (MBLs):** Confer resistance to carbapenems, inherent chromosomal (eg Stenotrophomonas maltophilia) versus plasmid acquired (eg New Delhi metallo-beta lactamases [NDM]).

Box 1

associated with toxicity and can have less effective pharmacokinetic and pharmacodynamic profiles.

The incidence of drug resistance can be reduced by diligent antibiotic stewardship. Although initial use of broad-spectrum agents may be required, therapy should be switched to organism specific narrower-spectrum therapy as soon as possible. This is why sample acquisition, rapid lab analysis and close liaison with local microbiology teams are so vital.

Diagnosis

The key to optimal management of nosocomial infection is timely diagnosis with a focus on use of targeted antimicrobial therapies.

This will not only improve patient outcomes, but will generally decrease the selection pressures, which lead to antimicrobial resistance. One of the most useful tests performed in the ICU is a correctly performed blood culture. Correct timing is particularly vital. Cultures performed after new antibiotics have been started loose sensitivity. Currently, only around one-third of patients displaying signs of sepsis show positive blood cultures. This can be due to containment of the infection, insufficient blood volume sampling, poor timing or administering antibiotics before sampling. Other specific diagnostic tools are discussed in later sections.

Preventing nosocomial infection

There is conclusive evidence showing that prevention of infection is far more effective than treatment. Measures to prevent nosocomial transmission can be hospital-wide or specific to ICU.

Hospital measures

In the UK, every health board has an assigned infection control team that reports directly to the chief executive. It is responsible for staff education and implementing infection control policies which are specific to local epidemiology.

Unsurprisingly, poor hand hygiene is thought to be responsible for 40% of all hospital-acquired infections. Improved compliance is associated with a reduction in transmission of infection. Doctors, especially, are least compliant with hand hygiene protocols. Protective garments are advised for any healthcare worker exposed to bodily fluids (e.g. blood, urine, oropharyngeal fluids). Isolation rooms are advised for patients with MRSA, C. diff, VRE and resistant Gram-negative organisms.

A UK wide surveillance system collects data of all nosocomial infections in the hospital and aims to compare nationwide rates. This then allows targeted protocols to be delivered where needed. This system uncovered in 2002 that two thirds of all hospital episodes of bacteraemia were associated with intravascular devices; with central venous catheters being the most common source. It identified 3.5 episodes of bacteraemia per 1000 admissions to hospital, compared to 9.1 per 1000 admissions to ICU.[4]

Methods of prevention in ICU

In addition to the aforementioned measures, a multidisciplinary approach is vital to good antimicrobial stewardship in the critical care environment (Box 2). Ongoing liaison between critical care physicians, microbiologists and pharmacists helps reduce unnecessary use of broad-spectrum therapies, evolution of less resistant organisms, and improves individual treatment for each patient with life-threatening sepsis.

Principles of antimicrobial stewardship in ICU

- Local knowledge of antimicrobial trends
- Early targeted therapy for sepsis, including antifungals in patients at higher risk
- Early source control (eg changing of central venous catheters)
- Appropriate de-escalation of broad-spectrum therapies
- Using shorter duration of antibiotics
- Appropriate dosing of antimicrobials

Box 2

Recently, infection control *care bundles* have been introduced to reduce nosocomial infection, particularly in relation to invasive procedures. These bundles group together a list of ‘best practices’ when inserting or maintaining an invasive device. These simple practices, when grouped together, have a synergistic effect in improving clinical outcomes.

The PROHIBIT trial[5] is the first multinational randomized multicenter trial studying the rate of catheter related blood stream infection (CRBSI) after CVC insertion when both a hand hygiene and best practice *care bundle* are used. This trial of over 3500 episodes of central line insertion demonstrated a decreased rate of CRBSI from 2.4/1000 CVC days to 0.9/1000.

Specific infections

Ventilator-associated pneumonia

Ventilator-associated pneumonia is a subset of hospital-acquired pneumonia (HAP) that occurs over 48 hours after endotracheal intubation. Around 15% of ICU patients are clinically diagnosed with VAP, although lack of a gold standard definition leads to both under and over diagnosis. It is associated with a significant morbidity and 20–30% attributable mortality. This can be reduced to approximately 9% with optimum treatment. The high mortality is likely due to the severity of the patient’s overall condition at the time of acquiring VAP. The treatment of VAP accounts for nearly half of all antibiotics given in ICU.[6] Ventilator-associated tracheobronchitis (VAT) is thought to be a precursor to VAP (when no chest X-ray changes are present). It is unclear whether this condition requires treatment or not.

Clinical suspicion of VAP should prompt the initiation of broad-spectrum antibiotics only after a quantitative invasive or non-invasive sample is taken for culture. The daily risk of developing VAP peaks within the first week of endotracheal intubation. Close attention to prevention measures and clinical signs of infection during this period is vital.

The initial step in its pathogenesis is the colonization of the upper respiratory tract with potentially pathogenic organisms including *Pseudomonas* and *Escherichia coli*. Microaspiration of these microbes either through the endotracheal tube or through a leak around the cuff allows them to enter the lower respiratory tract. This, combined with impaired host immunity, results in clinically active infection. Aspiration of gastrointestinal microbes also contributes, but less so. Mechanically ventilated patients at the highest risk of VAP are those aged 70 years or greater, those with existing lung disease, neurological injury and reduced level of consciousness, and clinical evidence of aspiration.

The widespread use of non-invasive ventilation has reduced the need for intubation and mechanical ventilation in a population of patients thought to be at risk of VAP. Other methods to reduce duration of intubation, including daily sedation holds, protocolized weaning and daily assessment of appropriateness for extubation have also reduced the incidence of VAP.

Methods to prevent microaspiration of microbes improve outcomes. Firstly, placing the patient in a semi-recumbent position reduces VAP incidence when compared to nursing the patient supine. This is particularly relevant in patients receiving enteral nutrition. The use of endotracheal tubes that allow aspiration of subglottic secretions reduces VAP occurrence as well.[7] Finally, silver-coated tubes prevent the transmission of oropharyngeal flora to the distal lung. These endotracheal tubes are associated with a 48% relative risk reduction of VAP, but so far have demonstrated no difference in patient-centred outcomes.

Modulation of flora colonizing the upper respiratory tract can also be used. Several small studies have evaluated the use of probiotics via the nasogastric or oropharyngeal route but all have been underpowered to evaluate changes in patient outcomes.

Multiple studies have demonstrated that selective decontamination of the digestive tract (SDD) reduces the incidence of VAP. Most SDD regimens involve the topical application of antimicrobial agents (e.g. tobramycin, amphotericin B) in the oropharynx and via the nasogastric tube. This is done with the aim of selectively eradicating pathogenic organisms without altering potentially beneficial anaerobic flora. However, the adoption of this technique has been limited, especially in the UK, due to concerns about an increase in rates of antibiotic resistance. Chlorhexidine oral care is routinely used as a similar preventative method. However, recent studies have questioned its safety, suggesting that oral chlorhexidine may increase patient mortality. The biological explanation of this finding remains under investigation but may be due to chemical lung damage caused by the aspiration of chlorhexidine.

Today, many of these preventative interventions are combined in VAP care bundles (Box 3).

The diagnosis of VAP is currently based on clinical, radiological and microbiological criteria. Radiological features, plus two of fever, leukocytosis or purulent secretions, has a sensitivity of 69% and specificity of 75% for VAP diagnosis Microbiological specimens can be obtained via broncheo-alveolar lavage (BAL) or the less invasive mini-BAL. The diagnostic threshold for BALs is 10^4 colony-forming units per millilitre (CFU ml^{-1}). Positive microbiological samples cannot differentiate between colonization and active infection. However, negative cultures from good quality sampling can reliably exclude VAP. The balance between the risk and cost of obtaining good quality invasive BAL samples and the benefits of improved patient outcomes needs to be assessed for each unit and each patient.

Management of VAP includes early antimicrobial therapy guided by close liaison with microbiology specialists, along with appropriate de-escalation and refined targeting as culture sensitivities emerge. A total duration of 5–7 days of effective therapy is appropriate for most organisms. Ten to 14 days is commonly used for resistant organisms or to treat *Pseudomonas*.

Example of a VAP care bundle

- Elevating the head of the bed 30–45 degrees
- Daily sedation holds
- Weaning plan
- Chlorhexidine oral care
- Stress ulcer prophylaxis
- Venous thromboembolism prophylaxis

Box 3

Central line-associated bloodstream infection

Infection occurs in around 3% of central line insertions. Central line-associated bloodstream infection is associated with a 19% mortality.[8]

CLABSI is more likely in patients with burns, immunosuppression, malnutrition, and those receiving TPN. Femoral central venous catheters (CVC) have higher rates of infection compared to internal jugular ones. Subclavian catheters have the lowest rates of infection.

Immediately after insertion, the catheter becomes coated in plasma proteins, including fibrin. Bacteria can migrate from the skin along the surface of the catheter, becoming fixed in this fibrin sheath. This can happen mere hours after initial insertion. There is probably a lag period of 3–4 days where the risk of CLABSI is low. Bacteraemia then becomes much more likely once a threshold count of bacteria is reached. Infection occurring within the first week is likely due to poor asepsis during insertion. After 7 days, any infection occurring is most likely due to intraluminal transmission of microbes following catheter handling.

The criteria for diagnosing CLABSI are:

- presence of CVC
- signs of catheter insertion site infection
- clinical signs and symptoms of bacteraemia
- resolution of symptoms after removal of CVC
- positive blood culture
- culture of the same bacteria from the CVC.

Clinically, diagnosis is made based on only a few of these criteria. The gold standard involves positive blood culture isolating the same organism as the CVC itself. There is no strong evidence supporting drawing cultures from every lumen of the CVC.

If infection is suspected, the central line should be removed as soon as possible.

Management should always be focused on culture sensitivities. Initially, a broad-spectrum beta lactam can be used for treatment. In patients at high risk of candidaemia, empirical fluconazole therapy is also reasonable. *S. aureus* bacteraemia will usually require the addition of a glycopeptide antibiotic unless the culture is proven to be meticillin-sensitive. This will also require a prolonged 14 day course of antibiotics, in addition to echocardiography to exclude infective endocarditis. Candidaemia requires 14 days of therapy and ophthalmological investigation to exclude endophthalmitis.

Paying close attention to strict asepsis during line insertion can help prevent CLABSI. The use of 2% chlorhexidine and avoidance of the femoral site insertion, where possible, will reduce infection rates. Any lines inserted in an emergency should ideally be replaced within 48 hours under full aseptic conditions. Continual audit and surveillance of CLABSI within the ICU helps focus the team on prevention. A combination of best practices into a care bundle can drastically reduce rates of infection related to CVC insertion (Box 4).

Catheter-associated urinary tract infection

Catheter-associated urinary tract infection (CA-UTI) refers to the presence of urinary infection in a person who is simultaneously catheterized, or had been so within the previous 48 hours. Pathogens tend to originate from the urethral meatus, travelling

Example of a central line insertion and care bundle[9]

- Trained operator
- Written record of procedure
- Surgical scrub
- Maximal sterile barrier precautions (hat, gown, gloves, mask)
- Aim to avoid femoral insertion site if possible
- Skin asepsis with 2% chlorhexidine in 70% isopropyl alcohol. Allow this to dry prior to skin puncture
- Use a sterile, transparent, semi-permeable dressing to cover the catheter site

Box 4

up the catheter on its external surface. Around one-third of pathogens travel intraluminally, originating from a contaminated collecting bag.

The European Centre for Disease Prevention and Control found in 2016 that 48 hours after ICU admission, 3% of patients had evidence of a UTI; 98% of these episodes were related to the presence of a urinary catheter; *E. coli* was the most frequently isolated organism.[10] *Candida* can be found in a urine culture, but most often represents colonization in a patient who has been given broad-spectrum antibiotics for another indication.

Diagnosing true pathogen infection from colonization can be difficult. Both the presence of increased inflammatory markers and evidence of organisms on Gram stain support the diagnosis of an infection.

Seven days of antibiotic treatment is usually sufficient, but up to 14 days in late responders may be required. An asymptomatic candiduria only requires a catheter change.

Many methods have been studied aiming to reduce nosocomial UTI in patients managed in ICU. Introduction of a daily nursing checklist to confirm the necessity of a urinary catheter reduces the number of catheter days, but is not associated with a significant decrease in CA-UTI. Introduction of a nurse-led urinary catheter removal protocol found that catheters were being kept in for shorter durations and infection rates were reduced. There is no evidence to support the use of prophylactic antibiotics for urinary catheter insertion or removal.

Multiple studies have demonstrated a reduction in nosocomial infections with the introduction of *urinary catheter care bundles*.[11] Strict asepsis for insertion, aseptic maintenance, regular review and prompt removal of catheters have been a mainstay of care for the last three decades in ICU. However, these best practices have not been used consistently together. Care bundles aim to ensure that this happens.

Conclusion

In conclusion, nosocomial infection is a significant cause of morbidity, mortality, and extended length of stay within the ICU. Due to the patient profile, and frequent use of invasive devices, intensivists encounter over double the amount of hospital-acquired infection in critical care compared to practitioners in the rest of the hospital. A third of these infections are preventable. The introduction of a collection of best practice care bundles for each invasive device assimilates all interventions that have been proven to improve outcomes. These bundles have shown promising rates of success. ◆

REFERENCES

1 Vincent JL, Bihari D, Suter P, et al. The prevalence of nosocomial infection in intensive care units in Europe. EPIC study. *J Am Med Assoc* 1995; **274:** 639–44.

2 Vincent JL. Nosocomial infections in adult intensive care units. *Lancet* 2003; **361:** 2068–77.

3 Appelgren P, Hellström I, Weitzberg E, et al. Risk factors for nosocomial intensive care infection: a long-term prospective analysis. *Acta Anaesthesiol Scand* 2001; **45:** 710–9.

4 Nosocomial Infection National Surveillance Service (NINSS). Surveillance of hospital acquired bacteraemia in English hospitals 1997–2002. London: Public Health Laboratory Service, 2002.

5 van der Kooi T, Sax H, Pittet D, et al. Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections. *Intensive Care Med* 2018; **44:** 48–60.

6 Hunter JD. Ventilator associated pneumonia. *BMJ* 2012; **344:** e3325.

7 Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. *Am J Respir Crit Care Med* 2010; **182:** 910–7.

8 Fletcher SJ, Bodenham AR. Catheter-related sepsis: an overview—part 1. *Br J Intensive Care* 1999; **9:** 47–53.

9 Scottish Intensive Care Society Audit Group. Central line insertion bundle version 2.0, 2012.

10 European Centre for Disease Prevention and Control. Annual Epidemiological Report 2016 – healthcare-associated infections acquired in intensive care units.

11 Marra AR, Sampaio Camargo TZ, Goncalves P, et al. Preventing catheter associated urinary tract infection in the zero-tolerance era. *Am J Infect Contr* 2011; **39:** 817–22.

FURTHER READING

Hellyer Ewan, Wilson Simpson. The Intensive Care Society recommended bundle of interventions for the prevention of ventilator-associated pneumonia. *J Intensive Care Soc* 2016; **17:** 238–43.

Vincent JL, Rello J, Marshal J, et al. International study of the prevalence and outcomes of infection in intensive care units. *J Am Med Assoc* 2009; **302:** 2323–9.