The Intensive Connection

Infection prevention and control

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Second Edition

Systemic Inflammation and Sepsis

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Second Edition 2018

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Update Info

Learning Objectives

After studying this module on **Infection prevention and control**, you should be able to:

- Understanding the scale of nosocomial infection and antimicrobial resistance
- Recognition of nosocomial colonisation and infection
- Infection control management
- Prevention of nosocomial infection and antimicrobial resistance

eModule Information

COBATrICe competencies covered in this module:

Competencies

- Obtains appropriate microbiological samples and interprets results
- Including the following Disorders: Respiratory, Cardiovascular, Neurological, Renal & Genito-Urinary, Gastrointenstinal, Haematological & Oncological, Infections, Metabolic, Endocrine
- Recognises and manages the septic patient
- Manages antimicrobial drug therapy

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1. Introduction

Healthcare-associated (nosocomial) infection and the emergence of resistant micro-organisms are major concerns for healthcare systems worldwide.

Infection is a major cause of critical illness and infection acquired in the ICU prolongs ICU stay and increases mortality. Critically ill patients are also highly susceptible to nosocomial infections. Frequent use of antibiotics contributes to selection pressure for resistant organisms, which may then become transmitted to other patients, wards and even hospital areas following patient discharge. A proper understanding of the mechanisms and means of prevention of nosocomial infection is therefore a basic component in the training and daily professional practice of all intensivists.

This module reviews the scale of the problem of antimicrobial resistance and nosocomial infection, the methods for recognising and detecting infection, and their management and prevention. The module will focus on the acutely unwell patient primarily in the context of critical care, but the general principles are applicable throughout the healthcare system. It will also place particular emphasis on antibiotic stewardship and the responsibilities of both individuals and organisations in preventing these conditions which cause significant morbidity and mortality.

2. Understanding the scale of nosocomial infection and antimicrobial resistance

2. 1. Epidemiology

2. 1. 1. Incidence and aetiology of nosocomial infection

Infection and sepsis are growing problems for healthcare systems. In the USA, of 750 million hospitalisations over a 22 year period, sepsis accounted for 1.3% of all hospitalisations, with three times the incidence in 2000 compared to 1979. Each year more than 2.5 million cases of Health Care Associated Infections (HAI) occur in Europe. These HAIs are responsible for 501 disability–adjusted Life Years (DAILYs)/100.000 inhabitants/year occurred in Europe. The observed DAILYs covered cognitive dysfunction, renal failure, physical impairment, pain and post-traumatic stress disorder, which might persist lifelong in a significant number of patients In addition, the incidence of nosocomial infection with resistant pathogens is increasing, particularly in critical care areas (intensive and high dependency care). ICU patients are more likely to develop a nosocomial infection during their stay than ward patients, with a prevalence rate of around 24 per 100 patients in the UK. A recent survey in the paediatric population in the USA showed that sepsis is the leading cause of death in infants and children, with 42 000 children with severe sepsis annually. Half of these are infants, and half of the infants are low or very low birth weight babies.

Critical illness is frequently precipitated or worsened by infection. The 2005 European Sepsis Occurrence And Prevention two-week period prevalence study in 198 European ICUs found that 24.7% of ICU admissions had sepsis on admission, 37% were septic during their stay and 64% received antibiotics whilst in the ICU. EPIC II was a 1-day, prospective, point prevalence study that collected demographic, physiological, bacteriological, therapeutic, and outcome data for 14 414 patients in 1265 participating ICUs from 75 countries with an analysis of 13 796 adult (>18 years) patients. It demonstrated that 51% were considered infected and 72% were on antibiotics. These studies suggest that prevalence of infection in ICU is increasing. In 2017 another point prevalence data capture exercise took place for EPIC III.

In text References

(Eggimann and Pittet. 2001; Centers for Disease Control and 2004; Thompson 2004; Healthcare Infection Society) 2006; Watson and Carcillo. 2005; Vincent et al. 2006; Vincent et al. 2009; Cassini et al. 2016)

Nosocomial infection rates vary between countries and centres. Common sites of infection are the respiratory tract, blood stream, gastrointestinal tract, and urinary system. The majority of nosocomial infections are device- or intervention-related: vascular catheters (arterial and venous), endotracheal tubes, intracranial shunts/monitors and urinary catheters. Quoted rates range from 4.9 to 17.4 bloodstream infections (BSI) per 1000 central venous catheter days, 4.4 to 46 cases of pneumonia per 1000 mechanical ventilator days, and 4.62 to 28 urinary tract infections (UTI) per 1000 urinary catheter days.
In paediatric intensive care units, primary bloodstream infections accounted for 28% of nosocomial infections, pneumonia for 21% and urinary tract infections for 15%. The distribution of infectious sites differed with age. The rate of catheter-related bloodstream infections (CRBSI) was higher in PICUs than adult ICUs whereas ventilator-associated pneumonia and catheter-associated urinary tract infections were less than those reported in adults.

According to EPIC II, the respiratory tract is the most common site of infection

- Respiratory tract - 64%
- Abdomen - 20%
- Bloodstream - 15%
- Renal Tract / Genitourinary System 14%

Other possible sites for nosocomial infections in critical care and in acutely unwell patients include:

- CRBSI
- Surgical site infections
- Intestinal infections – Clostridium difficile
- Cerebrospinal fluid infection (e.g. in neuro-critical care)
- Infective endocarditis.

Which micro-organisms typically cause catheter-related bloodstream infections?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Although all multi-drug resistant (MDR) pathogens may produce CRBSI, pathogens which colonise the skin of critically ill patients are most common. These would include coagulase-negative Staphylococcus, Staphylococcus aureus, Gram-negative pathogens (e.g. Pseudomonas sp., E. coli), Candida and Enterococcus.

What factors influence your initial choice of antibiotics for CRBSI?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Initial empirical choice of antibiotics for CRBSI will depend on local prevalence of the above organisms. Until microbiological data become available from the blood cultures and the removed catheter tip, a broad-spectrum antimicrobial such as a carbapenem, piperacillin-tazobactam or third-generation cephalosporin, with strong consideration of a glycopeptide such as vancomycin, would be a suitable choice. In patients with risk factors for fungal infection consider fluconazole in addition.

In text References

(Richards et al. 1999; Lizan-Garcia et al. 2006; Calandra, Cohen and International Sepsis Forum Definition of Infection in the ICU Consensus. 2005; Division of Reproductive and National Center for Chronic Disease Prevention and Health 2006; ESICM 2017)

2. 1. 2. Epidemiology of infections in the critically ill

Infection in critically ill is common in European ICUs and EPIC II reported a 51% infection rate. The situation in Europe displayed large variations. The most likely causes are:

- Differences in antimicrobial use
- The presence (or absence) of infection prevention & control policies
- Variations in healthcare utilisation practices

International comparisons showed Central and South America had the highest infection rate (60%), Asia 52%, North America 48% and Africa 46%.
EPIC II also showed that the commonest bacterial isolates were gram-negative (62%), followed by gram-positive (47%) and 19% fungal. Furthermore, the nature of the gram negative pathogens is concerning as there has been a growth in the proportion of resistant bacteria in these.

2. 1. 3. Microbial ecology in the acutely ill patient

The proportion of Gram-positive and fungal nosocomial infections is increasing. Gram-positive infections are now slightly more common than Gram-negative infections.
The most common organisms involved in nosocomial ICU infections are

- Gram-positive bacteria
    - Methicillin-sensitive Staphylococcus aureus (MSSA)
    - Methicillin-resistant Staphylococcus aureus (MRSA)
    - Coagulase-negative staphylococci
    - Enterococcus (a proportion of which are vancomycin-resistant)
    - Clostridium difficile
- Gram-negative bacteria
    - Pseudomonas aeruginosa
    - Enterobacteriacea (may be multi-resistant, including ESBL-producing)
        - Escherichia coli (some of which are extended spectrum beta-lactamase (ESBL)-producing)
        - Klebsiella spp. (some of which are ESBL-producing)
        - Enterobacter spp.

- Serratia spp.
  - Stenotrophomonas maltophilia
  - Acinetobacter
- Anaerobes
  - Both Gram-positive and Gram-negative organisms
- Fungi
- Candida albicans
- Candida (non-albicans)

Of particular concern is the increasing incidence of resistant pathogens infecting acutely ill patients. These include: MRSA, coagulase-negative Staphylococcus, vancomycin-resistant enterococci (VRE), ESBL-producing and/or carbapenem resistant *Klebsiella*, *Enterobacter*, *P. aeruginosa*, *Acinetobacter* and *Stenotrophomonas maltophilia*.
In some countries summarised third generation chepalosporin resistant (3GC) enterobacteriaceae (*Klebsiella spp*, plus *E. coli* and *Enterbacter spp*.) are more common than MRSA.

In paediatric intensive care units, the most commonly reported pathogens in BSI: coagulase-negative staphylococci (38%), followed by enterococci and *S. aureus*. Gram-negative bacilli were found in 25%, Enterobacter spp. being the most commonly reported species. In nosocomial pneumonia, P. aeruginosa and S. aureus were most commonly found.

Note

Multi-drug resistant pathogens are significant causes of nosocomial infection within hospitals and particularly within intensive care units.

In text References

(Vincent et al. 2009; Meyer et al. 2013; European Centre for Disease Prevention and 2017; Maechler et al. 2015)

2. 1. 4. Risk factors for nosocomial infections

There are a number of risk factors for the development of nosocomial infections in the acutely unwell or critically ill patient and also a number of risk factors which predispose to the development of multi-drug resistant pathogens in these patients.

Table 1: Risk factors for the development of nosocomial infections

Related to underlying health status	Related to acute disease process	Related to invasive procedures	Related to treatment
• Advanced age • Malnutrition • Alcoholism • Heavy smoking • Chronic lung disease • Diabetes • Liver cirrhosis • Renal insufficiency	• Surgery • Trauma • Burns	• Endotracheal or nasal intubation • Central venous catheterisation • Extracorporeal renal support • Surgical drains • Nasogastric tube • Tracheostomy • Urinary catheter	• Blood transfusion • Recent antimicrobial therapy • Immunosuppressive treatments • Stress-ulcer prophylaxis • Recumbent position • Parenteral nutrition • Length of stay • Deep sedation

The impact of these general factors is modified by more specific risk factors for certain infections. The impact of organisational aspects must not be underestimated. Several studies have shown that overcrowding on ICU or understaffing of ICU correlates with increased nosocomial infections. This may be due to pressures on individuals' workload resulting in sub-optimal infection control procedures, such as hand washing, donning of aprons and care of central venous catheters (CVCs). This encourages cross transmission of pathogens between patients via staff members.

More severely ill patients are susceptible to nosocomial infections due to a relative immunodeficiency (such as the immunoparesis seen in sepsis). The breaching of natural body defences with invasive devices (such as endotracheal tubes, CVC, urinary catheters, ICP bolts) promotes this. Scoring systems such as APACHE II/III or SAPS II / III allow some quantification of illness severity but it must be borne in

mind that the systems were designed for mortality prediction in populations, and perhaps sequential organ failure scores such as SOFA and qSOFA may be more appropriately used (Sepsis-3).

Specific nosocomial infections also carry specific risk factors. For example risk factors for ventilator associated pneumonia (VAP) include unnecessary deep sedation, lack of weaning protocols and spontaneous breathing trials, enteral feeding, use of stress ulcer prophylaxis, re-intubation and prolonged ventilation.
The majority of CRBSIs are associated with CVCs and are the most common cause of nosocomial bacteraemia. In prospective studies, the relative risk for CRBSI is up to 64 times greater with CVCs than with peripheral venous catheters, but a high rate of peripheral catheters generates relevant number of nosocomial infection. CVCs pose a greater risk of device-related infections than any other type of medical device. Risk factors for CRBSI include underlying disease, method, site and duration of insertion, the administration of parenteral nutrition, dialysis and local risk factors such as personal hygiene, colonisation and contiguous infections.

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2. 2. Nosocomial infections

2. 2. 1. Factors accounting for geographical variation

2. 2. 1. 1. Antimicrobial usage

Use of anti-microbials within a nation will markedly influence the evolution of multi-drug resistant (MDR) pathogens. Physician usage of antimicrobials within the hospital setting will impact on the development of resistant strains, but the bulk of antimicrobial usage in most nations is at the community and primary care level. The availability of antimicrobial classes for the use of primary care physicians will play a part in the development of resistance in the long term as will the availability of over the counter antimicrobials in some nations. Self-medication by patients may be inappropriate, may be inadequate in terms of duration or dosing, and may be influenced by advertising or

the media or availability on the internet. Even in settings where antimicrobials are prescription only, prescribing practices may be influenced by patient expectation and cultural attitudes, putting pressure on physicians. Patients may be poorly compliant and courses not taken appropriately. In some countries patients may be unable to afford the full course.

Veterinary prescription of antibiotics also accounts for a degree of resistance and that varies between nations. In Europe about half of all antibiotics are used in animals producing food, including poultry. Most are used for either prophylaxis or growth promotion. Inevitably these will be at sub-therapeutic doses. Examples are glycopeptides and streptogramins used as growth promoters and fluoroquinilones used in a similar fashion in poultry. Vancomycin use in the 1990s had promoted the emergence of VRE in the community until legislation in Europe in 1997 stopped its use as a growth promoter. The VRE rates in animals and food fell sharply after this.

Infection control practices vary between nations from very aggressive search and destroy tactics to less intensive measures, such as isolation and cohorting. Other measures related to regulation of antibiotic use in hospitals are discussed later.

2. 2. 1. 2. Demographics

Urbanisation is altering the spectrum of disease witnessed in nations with increasing incidence of pneumonia and respiratory tract infections. The aging population has meant growing proportions of the first world population needing hospitalisation and exposure to anti-microbial therapy and MDR pathogens in hospital which may then disseminate out to form community reservoirs. Increasing travel between nations coupled with migration from less affluent to more affluent areas has encouraged dissemination of resistant strains.

See also Academy module on Sepsis and Septic Shock and Academy module on Immunocompromised patients.

In text References

(Shankar-Hari et al. 2016; Gahlot et al. 2014; Girard et al. 2010; Klompas et al. 2016)

2. 2. 2. Impact of Nosocomial Infection on Morbidity and mortality

Nosocomial infections are associated with, and independently contribute to, serious adverse events, including

- Increased use of antimicrobials and associated adverse effects
- Development of sepsis, severe sepsis or septic shock
- Susceptibility to further infections (notably fungal infection)
- Additional medical interventions
- Increased duration of ventilation
- Increased length of stay
- Death

Although large epidemiological studies show that the overall mortality from severe infections and sepsis is decreasing for hospital admissions as a whole (from 27.8% in the early 1980s to 17.9% in the late 1990s), the crude number of deaths has risen because more patients are at risk.

Between 7-10 percent for hospitalised patients succumbed to nosocomial infection (WHO). The endemic burden of health care-associated infection is also significantly higher in low- and middle-income than in high-income countries, in particular in patients admitted to intensive care units and in neonates. As is the case for many other patient safety issues, nosocomial infections create additional suffering and come at a high cost for patients and their families.

Infections prolong hospital stays, create long-term disability, increase resistance to antimicrobials, represent a massive additional financial burden for health systems, generate high costs for patients and their family, and cause unnecessary deaths. Such infections annually account for 37,000 attributable deaths in Europe and potentially many more that could be related, and they account for 99,000 deaths in the USA.

Annual financial losses due to health care-associated infections are also significant: they are estimated at approximately €7 billion in Europe, including direct costs onlyand reflecting 16 million extra days of hospital stay, and at about US$ 6.5 billion in the USA.

In one retrospective non-ITU study, multidrug-resistant gram-negative bacteria were associated with a significantly elevated risk of mortality both for invasive (RR, 2.32; 95% CI, 1.85–2.92) and noninvasive cultures (RR, 1.33; 95% CI, 1.22–1.44) during the 30-day period. Similarly, patients with MRSA HAIs (RR, 2.77; 95% CI, 2.39–3.21) and colonisation (RR, 1.32; 95% CI, 1.22–1.50) had an increased risk of death at 30 days.

In the EPIC II study, MRSA group showed 8.6% and 9.4% higher ICU and hospital mortality (absolute difference) compared to MSSA group. Both clinically and statically significant observation.

Despite obvious, attributable mortality due to nosocomial infections in critical care units, it remains difficult to prove. In propensity matched groups ICU-acquired candidemia in critically ill patients is not associated with an increase in either ICU or hospital mortality.

In text References

(European Centre for Disease Prevention and 2017; Vincent et al. 2009; Shah et al. 2016; World Health 2018; Nelson et al. 2017; Girard et al. 2010; Klompas et al. 2016; González de Molina et al. 2012)

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2. 3. Multi-drug resistant pathogens

2. 3. 1. Gram-positive organisms

2. 3. 1. 1. Methicillin-resistant Staphylococcus aureus

Methicillin-resistant Staphylococcus aureus (MRSA) was first cultured in 1960, only one year after the introduction of methicillin into clinical practice. It is thought that it evolved by the acquisition of a genetic element, the staphylococcal cassette chromosome mec (SCCmec). In addition to the penicillins and cephalosporins to which Staphylococcus aureus has established resistance, SCCmec also enables development of resistance to non-β-lactam antibiotics.

The incidence of MRSA infections varies widely across Europe; overall around 30% of S. aureus are resistant, but this ranges from close to zero in the Netherlands which has an intensive screening and isolation policy, to more than 50% in some other countries. In addition, there is a growing community reservoir throughout Europe, typically in long-stay facilities such as nursing homes.

Of greater concern is the emergence of strains which are either partially or fully resistant to glycopeptides, the glycopeptide intermediate-sensitivity S. aureus (GISA) or glycopeptide-resistant (GRSA). They typically occur in situations of large scale use of intravenous vancomycin over long periods.

What aspects of the Dutch healthcare system may result in the very low incidence of MRSA?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

A: Despite the fact the Netherlands is one of the most densely populated countries in Europe it has a low incidence of MRSA infections. This is due to a number of factors including infection control specialists, infection control nurses, high staff to patient ratios, spacious rooms and available isolation facilities, use of routine surveillance systems, antibiotic policies coordinated by infection control specialists and a ‘search and destroy’ policy for MRS This involves strict isolation of transfers and MRSA carriers and aggressive use of decolonisation regimes for staff and patients. The relatively low hospital occupancy rates facilitate the flexibility which is required to allow these measures to be put into effective practice.

2. 3. 1. 2. Coagulase-negative staphylococci

Coagulase-negative staphylococci (CNS) are staphylococci unable to coagulate blood plasma and are distinguished from S. aureus by this feature. They are also less pathogenic than S. aureus. There are around 15 species indigenous to humans, classified as novobiocin-sensitive or novobiocin-resistant (S. saprophyticus). Most species are normal commensals which act opportunistically to produce infection, typically in CRBSI. They account for up to 19% of ICU-acquired infections as a consequence. In PICUs, CNS account for 38% and in neonatal ICUs 48% of BSI. Most (90%) of CNS are resistant to methicillin and are also resistant to aminoglycosides. Susceptibility to vancomycin remains high and the incidence of resistance is very low although it can occur.

2. 3. 1. 3. Vancomycin-resistant Enterococcus

Enterococci are Gram-positive cocci which are part of the normal flora of the gastrointestinal tract. The majority of infections are caused by two species, Enterococcus faecalis and Enterococcus faecium. Vancomycin resistance began to occur in the late 1980s and now a quarter of enterococci infections are due to vancomycin-resistant Enterococcus (VRE) in the USA. The incidence is lower, but rising rapidly in Europe. The resistance is due to the van gene cluster, of which vanA and vanB are the most common.
There is an association between the incidence of VRE colonisation and the use of vancomycin, cephalosporins and anti-anaerobic agents (e.g. metronidazole, imipenem). When this allows colonisation rates of VRE to exceed 50%, this creates colonisation pressure and other risk factors become unimportant as spread from colonised patients becomes the only significant factor.
Due to its extensive intrinsic resistance, the antibiotic treatment of VRE can be difficult. High dose ampicillin can be used in many cases, while other choices may include quinupristin/dalfopristin, linezolid or chloramphenicol. Vancomycin resistance is driven by widespread use of intravenous vancomycin which results in very low, sub-therapeutic, levels of vancomycin in the bowel lumen.

2. 3. 1. 4. Clostridium difficile

This sporulating toxin-producing Gram-positive anaerobe is a growing problem in hospital practice. Around 3% of the healthy population are carriers. Spores persist in the environment, and can colonise and cause infection in susceptible individuals, particularly the elderly, those exposed to (even single dose) broadspectrum antimicrobials, surgical patients, and the immunocompromised. Diarrhoea and vomiting can progress rapidly to life-threatening septic shock from pseudomembranous colitis, primarily (but not exclusively) limited to the colon. Treatment and control measures include enteral metronidazole (enteral vancomycin may also be used), isolation and handwashing, and meticulous environmental cleaning.

> **Warning**
>
> Handwashing with soap and water is specifically required to remove C. difficile spores which are resistant to alcohol hand disinfection.

In text References
(Cookson 2007)

2. 3. 2. Gram-negative organisms

Gram-negative organisms possess an outer cell membrane containing lipopolysaccharide (endotoxin). Antimicrobial resistance is conferred by a variety of mechanisms, in particular the extended spectrum β-lactamases (ESBLs), which permit resistance to a wide range of agents including non-β-lactam antibiotics and combination agents.

In text References

(Ghafourian et al. 2015)

2. 3. 2. 1. Pseudomonas spp

Pseudomonas spp. rarely cause disease in healthy individuals but are a common cause of severe sepsis and septic shock in patients immunocompromised for any reason. Pseudomonas aeruginosa readily colonises hospitalised patients (25% in the first week, 60% after two weeks). The organism is carried in the gastrointestinal tract by 10% of the normal population.
Pseudomonas spp. are intrinsically resistant to many antibiotics. This is due to multi-drug efflux pumps, an impermeable membrane in its cell wall and production of enzymes such as β-lactamase. Anti-pseudomonal agents include β-lactams with β-lactamase inhibitor combinations (such as piperacillintazobactam and ticarcillin-clavulanate), carbapenems (imipenem, meropenem), cephalosporins (ceftazidime, cefipime), fluoroquinolones, aminoglycosides and aztreonam.
Resistance to any of these drugs can develop via plasmid-mediated mechanisms or mutations, involving decreased permeability, increased efflux pumps or hyper-secretion of β-lactamase. However, most isolates are susceptible to the full range of agents. In about 10% of patients, resistance develops, most commonly with imipenem and least often with ceftazidime, piperacillin or ciprofloxacin. This has lead to interest in combination therapy for Pseudomonas infections, although there is little supporting evidence. Another option is antibiotic rotation (reviewed in Mechanisms of antibiotic resistance).

2. 3. 2. 2. Klebsiella spp

The majority of Klebsiella infections are opportunistic and nosocomial. It is an environmental pathogen which readily colonises the respiratory tract and skin, and is consequently often involved in ventilator-associated pneumonia (VAP) and less frequently in CRBSI. Typical risk factors for Klebsiella infection are long hospital stay, previous exposure to antimicrobials and presence of CVCs.
Klebsiellae are the likeliest of all the Enterobacteriaceae family to develop extended-spectrum β-lactamases. This is because ESBLs are primarily plasmid borne and Klebsiella display a predilection for acquiring plasmids. ESBLs hydrolyse third-generation cephalosporins and aztreonam as well as broad-spectrum penicillins. The ESBL plasmids also frequently code for genes conferring resistance to aminoglycosides and co-trimoxazole. About 25% of European isolates of Klebsiella carry an ESBL plasmid. The agents of choice are the carbapenems e.g. meropenem or imipenem. Aminoglycosides may also be useful.

2. 3. 2. 3. Stenotrophomonas maltophilia

Despite initial reports of low virulence, S. maltophilia (formerly Xanthomonas maltophilia) is an increasingly frequent multi-drug resistant (MDR) pathogen, infecting opportunistically in the critically ill. It may be involved in VAP, surgical site infection (SSI) or CRBSI. It has high intrinsic resistance to β-lactams due to two inducible enzymes. L1 is a β-lactamase with broad activity against penicillins, carbapenems and cephalosporins; and L2 is a cephalosporinase active against cephalosporins and monobactams. In addition, it is resistant to quinolones and aminoglycosides via modifying enzymes and energy dependent efflux pumps. As a result the pathogen is difficult to eradicate, with cotrimoxazole the agent of choice and ticarcillin-clavulanate the second choice.

2. 3. 2. 4. Enterobacter spp

Enterobacter species belong to the same family as Klebsiella and are opportunistic pathogens in the acutely unwell and debilitated patient. They may produce nosocomial infections at many sites, such as VAP, SSI, UTI and CRBSI. Most infections occur following prior colonisation, which in turn is predisposed to by prior exposure to antibiotics. Enterobacter species possess an inducible β-lactamase called AmpC. In certain mutants, this production is at very high levels and treatment with broad-spectrum β-lactam agents selects out these mutants. Carbapenems are best choice for Enterobacter infections and resistance to these agents is currently rare.
Similarly to Klebsiella, Enterobacter species can acquire an ESBL plasmid that confers additional resistance to quinolones and aminoglycosides.

2. 3. 2. 5. Acinetobacter

Acinetobacter baumanii is a Gram-negative coccobacillus that forms part of the normal flora of the skin, particularly in moist areas such as the groin and is carried in up to 25% of the population. It is a persistent organism in the environment and contamination of the area adjacent to infected or colonised individuals is problematic. It can cause a wide range of nosocomial infections such as pneumonia, CRBSI, UTI, SSI and meningitis. Its spread is typically from colonised individuals, such as healthcare workers or from contaminated equipment.
Acinetobacter is intrinsically resistant to many agents. These include broad-spectrum cephalosporins, penicillins, fluoroquinolones and aminoglycosides. This resistance is mediated by plasmid-mediated β-lactamases, chromosomal cephalosporinases, altered penicillin-binding proteins and membrane impermeability. Imipenem is the agent of choice for Acinetobacter infection and resistance is rare. The alternative is ampicillin-sulbactam (or amoxicillin-clavulanate).

2. 3. 3. Candida spp

Candida spp. are fungi (yeasts) which are normal colonising organisms of skin and gut. Critically ill patients are commonly (around 55% in some studies) colonised with Candida. Invasive infection is rare (around 2%), diagnosis difficult, and mortality of candidaemia high (35-65%). Common associations are antibacterial use, parenteral nutrition catheters, peritonitis, renal replacement therapy and cerebral shunts. Infection is thought to be endogenous on most occasions, but there are documented cases of cross-transmission, particularly of Candida tropicalis, in an ICU environment.
Most infections are caused by Candida albicans, which is sensitive to fluconazole (a widely-used azole anti-fungal agent). However, an increasing proportion is caused by other Candida spp., including C. krusei and C. glabrata, which are intrinsically resistant to fluconazole. Routine fluconazole prophylaxis could promote resistance. Candida glabrata possesses both intrinsic and rapidly developing acquired resistance. Rapid acquisition of stable azole resistance by Candida glabrata isolates was described before the clinical introduction of fluconazole. While other antifungal agents (including amphotericin, newer azoles like voriconazole, and echinocandins) may all be effective, information from resistance testing is usually not available routinely and the time taken for speciation of Candida may cause delays in initiating appropriate therapy. In this context, knowledge of the local flora and Candida identified from previous specimens from a patient might valuable.

In text References

(Perlin, Rautemaa-Richardson and Alastruey-Izquierdo 2017; Calandra et al. 2016)

Challenge

Make a list of all the micro-organisms identified in samples from patients in your ICU during the past week. Which are the most frequent? Can you use this list to predict the organisms which will appear in the next ten ICU patients?

How may we determine appropriate choices of empirical antibiotics when presented with an infection in a critically ill patient?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Although empirical antibiotics should ideally cover all the potential causes of the infection that may be compromising the patient's condition, their prescription does not supersede the essential concept of trying to identify the primary source of sepsis by careful attention to history and clinical examination. Identification of the likely source of sepsis by such basic principles may influence the choice and dosage of empirical antibiotics administered.

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3. Mechanisms of antibiotic resistance

3. 1. Scale of the Problem of Antimicrobial Resistance (AMR)

AMR is present in all countries and is of global concern. It usually happens through genetic changes; however, inappropriate antimicrobial use in people and animals is accelerating this process. Of real concern is new resistance mechanisms emerging and spreading globally. Such threats reduce our ability to treat infections in some seriously ill patients, particularly in ICU patients, immunosuppressed and post-transplant patients. A further worry is the increasing incidence of resistant pathogens producing infection in the acutely unwell patient. These include: MRSA (10%), Coagulase negative staphylococcus, Enterococci (10.6%), Klebsiella (12.6%), Enterobacter (6.9%), P. aeruginosa (20%), Acinetobacter (8.9%) and Stenotrophomonas maltophillia. AMR contributes to 25,000 deaths per annum in the EU, globally it could be as high as 1,700,000. If current infection and resistance trends are not reversed WHO predicts 10 million deaths per annum between 2015 and 2050 with the largest numbers in Africa and Asia.

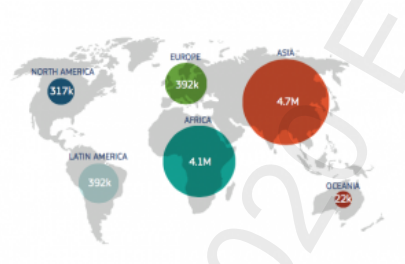

Figure 1: Deaths attributable to antimicrobial resistance per annum between 2015 and 2050. (Adapted from Review on Antimicrobial resistance, Antmicrobial resistance: tackling a crisis for the health and wealth of nations, Dec 2014)

In text References

(O'Neill 2014)

References

- O'Neill J, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, 2014, http://www.naturallivestockfarming.com/wp-content/uploads/2015/09/Antibiotics-UK-dec-2014-Review-paper-on-health-wealth1.pdf

3. 2. Mechanisms of antibiotic resistance

There are a number of mechanisms in which pathogens may become resistant to antibiotics. Some of these are intrinsic resistances and some are acquired resistances.

- Intrinsic resistance may be due to the lack of the molecular target for an antibiotic or membrane impermeability to the agent.
- Acquired resistance is principally due to one of four mechanisms: drug inactivation, reduced permeability, drug efflux or target modification.

3. 2. 1. Drug inactivation

Classic examples of this mechanism are the β-lactamases. These enzymes hydrolyse the beta-lactam ring found in penicillins and cephalosporins. There are several β-lactamases including those chromosomally-encoded or plasmid-mediated.
Initially found in Gram-positive species, the development of the enzyme in Gram-negative organisms has resulted in a wide range of resistance to penicillins and cephalosporins. Originally the plasmid-mediated β-lactamase TEM-1 was isolated in E. coli from which it

transferred to other Enterobacteriaceae and Pseudomonas. The enzyme inactivated penicillins but not cephalosporins. However the spectrum of activity has increased in some mutants and the plasmid-mediated ESBL enzymes have developed. One of the difficulties with this pattern is the variable susceptibility to individual agents with ESBL strains.

3. 2. 2. Reduced permeability

It is unusual for reduced permeability to act as a sole mechanism of resistance, but it typically acts synergistically with other mechanisms. Pseudomonas sp. and S. maltophilia both have relatively impermeable outer membranes and in certain strains of Pseudomonas spp. the loss of a porin channel (OprD) produces carbapenem resistance.

3. 2. 3. Efflux of drugs

Found primarily in Gram-negative bacteria, this mechanism involves active transport of the antibiotic molecule out of the pathogen via a pump. The mechanism can be highly specific or wide ranging in action. In Pseudomonas aeruginosa, the MexAB-OprM system confers resistance to penicillins, cephalosporins, chloramphenicol, tetracyclines and fluoroquinolones.

3. 2. 4. Alteration of molecular targets

The final mechanism is alteration in the molecular target of the antibiotic or creation of an alternative pathway. The production of a low affinity penicillin-binding protein (PBP2a) in MRSA and CNS is an example of altered targets. Vancomycin resistance in enterococci is encoded by the van genes and mediated by production of a new cell wall substrate, an example of an alternate pathway.

4. Risk factors for nosocomial infection

There are a number of risk factors for the development of nosocomial infections in the acutely unwell or critically ill patient in addition to those which promote the emergence of multi-drug resistant pathogens.

- **Patient**
  - Severity of illness
  - Shock on admission
  - Age >60 years
  - Neurological failure at day three on the ICU
  - Supine body posture in intubated patients
  - Immuno-incompetence
  - Burns
  - Major surgery
  - Low birth weight in paediatric population
- **Therapy**
  - Parenteral nutrition
  - Antimicrobial therapy
  - Central venous access
  - Days with arterial or venous cannula
  - Mechanical ventilation
  - Tracheostomy
  - ICP monitoring
  - Immunosuppression
- **Environment**
  - ICUs with high prevalence for resistant pathogen (> 25%)
  - Prolonged ICU or hospital stay
  - Medical provision in low income areas (Africa, Asia, Middle East, South and Eastern Europe)
  - Understaffing of unit
  - Bed occupancy rates
  - Inadequate infection control mechanisms, e.g. inadequacy of hand hygiene

Note

Intensive care patients have a number of risk factors for developing nosocomial infections that are additional to factors affecting patients in other areas of the hospital.

Many of these generic risk factors are evidently surrogates for underlying mechanisms. Instrumentation breaches body defences; low rate of compliance with hand hygiene and severity of illness may impair the immune system (for example, acute renal failure secondary to insults such as rhabdomyolysis or sepsis may impair the immune system). Most nosocomial infections also have specific risk factors, for example ventilator-associated pneumonia is promoted by deep sedation, , lack of spontaneous breathing trial and/or of weaning protocol and consecutive prolonged ventilation; bloodstream infections are promoted by low rate of hand hygiene and central venous catheter colonisation. The link between lapses in practice and subsequent infection is often remote and difficult to detect.

Think

Think of the last occasion you did not comply fully with an infection control guideline.

Warning

Have you ever removed a cap from a CVC connection, given an intravenous drug, and then replaced the same cap on the connector (plus your skin organisms)?

In text References

(Huskins et al. 2011; ESICM 2017; Huskins et al. 2011; Cook et al. 2002; Derde et al. 2014; Cohen, Cohen and Shang 2015; Roquilly et al. 2015; Pronovost et al. 2006; Kalil et al. 2016; Martin-Loeches et al. 2013)

References

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4. 1. Risk factors for acquisition of multi-drug resistant pathogens

Critically ill patients are also exposed to a number of inter-related risk factors that promote the acquisition of multi-drug resistant (MDR) pathogens as colonisers and causative pathogens. These include:

- Hospital exposure to broad-spectrum antibiotics: multiple courses, high doses, prolonged duration
- Large exposure to antibiotics in outpatients
- Prolonged length of hospital stay
- Chronic illness with dependence on staff and medical interventions.
- Exposure to pathogens in the healthcare environment

In the ICU, around 60% of patients are receiving antimicrobials at any given time, with virtually all being exposed at some point during their stay. This makes the ICU a natural environment for the selection of pathogens.

Patterns of antibiotic resistance and international variations

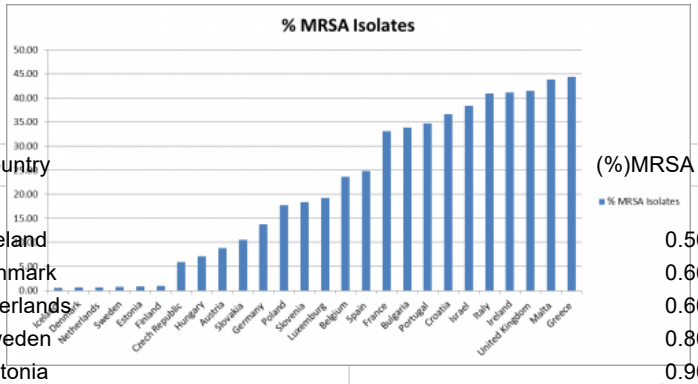
There is wide international variation in patterns of multi-drug resistance. In Europe, microbial resistance data is collected by the EARSS programme (European Antimicrobial Resistance Surveillance System) funded by the European Commission (see reference, below). This network connects national surveillance systems and provides comparable and validated results of routine antimicrobial susceptibility tests following standardised protocols from a representative set of laboratories per country.

In text References

(European Centre for Disease Prevention and 2017)

The figure below displays the national differences in MRSA rates across Europe from 52,364 staphylococcal blood culture isolates tested using PCR for the MecA gene or the resistance to oxacillin on oxacillin screening plates (minimum inhibitory concentration >4 mg/l; >2 for Denmark and Sweden).

Figure 2:



Country	(%)MRSA Isolates
Iceland	0.50
Denmark	0.60
Netherlands	0.60
Sweden	0.80
Estonia	0.90
Finland	1.00
Czech Republic	5.90
Hungary	7.10
Austria	8.80
Slovakia	10.50
Germany	13.80
Poland	17.70
Slovenia	18.40
Luxemburg	19.20
Belgium	23.60
Spain	24.80
France	33.10
Bulgaria	33.90
Portugal	34.70
Croatia	36.70
Israel	38.40
Italy	40.90
Ireland	41.20
United Kingdom	41.50
Malta	43.80
Greece	44.40

Figure 2: This analysis of national data shows substantial geographical variation in MRSA prevalence, with an approximate North to South gradient. However, this disguises marked local variation within many countries. Adapted from Tiemersma EW et al.

Think

What reasons can you identify to explain these variations in MRSA prevalence between countries? Do you think that the same reasons explain the variation within countries as well? Could the degree of variability within countries reflect reliability of healthcare processes?

References

- European Centre for Disease Prevention and Control, European Antimicrobial Resistance Surveillance Network (EARS-Net), 2017, https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net

4. 2. Factors accounting for variations in MDR micro-organisms

- Use of antibiotics
  - Within hospital settings
  - In the community
  - In animal husbandry
- Infection control procedures within hospitals
- Demographic factors: ageing population, chronic disease
- Degree of urbanisation and population density
- Patterns of migration / immigration and travel.

Most prescribing occurs in the community in primary care. In the developing world and in some developed countries, antibiotics can be purchased over the counter with no physician controls, and partial and inadequate treatment may be common. In North America and Europe about half of all antibiotics are used as growth promoters in animal husbandry; these include glycopeptides, streptogramins and fluoroquinolones. In 1997, European legislation banned the use of vancomycin for this purpose, and rates of VRE in animals and food rapidly declined.

Note

Antimicrobial usage is the single most important factor driving resistance.

In text References

(Bruyndonckx et al. 2015; European Centre for Disease Prevention and 2017; Onakpoya et al. 2018)

References

- Bruyndonckx R, Hens N, Aerts M, Goossens H, Cortiñas Abrahantes J, Coenen S, Exploring the association between resistance and outpatient antibiotic use expressed as DDDs or packages., 2015, PMID:25585511
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4. 3. Morbidity and mortality

Nosocomial infections are associated with, and independently contribute to, serious adverse events, including

- Increased use of antimicrobials and associated adverse effects
- Development of sepsis, severe sepsis or septic shock
- Susceptibility to further infections (notably fungal infection)
- Additional medical interventions
- Increased duration of ventilation
- Increased length of stay
- Death

Although large epidemiological studies show that the overall mortality from severe infections and sepsis is decreasing for hospital admissions as a whole (from 27.8% in the early 1980s to 17.9% in the late 1990s), the crude number of deaths has risen because more patients are at risk. There is a significant correlation between the prevalence rate of ICU-acquired infection and mortality rates.

In text References

(Eggimann and Pittet. 2001; Huskins et al. 2011; Kalil et al. 2016; Martin-Loeches et al. 2013)

Calculating the morbidity and mortality directly attributable to nosocomial infections can be difficult. Several epidemiological methods can be used:

- Estimation – a method whereby an experienced clinician subjectively estimates whether the death of a patient is related to the nosocomial infection
- Cohorting – one cohort with a nosocomial infection and one without are compared, with some attempt made to consider confounding variables
- Case control – infected and non-infected patients are matched for several confounding factors related to the parameter investigated (e.g. age, ethnicity, severity of illness, co-morbidities).

The attributable mortality (the surplus mortality caused by the nosocomial infection alone) is variably estimated to be between 4%-40%, depending on the type of infection, the method of estimation, and the population studied.

References

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5. Recognition of nosocomial colonisation and infection

5. 1. Surveillance of colonisation and infection

5. 1. 1. National and international surveillance systems

Most developed countries have established infection surveillance systems. Reporting is diverse, ranging from specific focused audits (e.g. bloodstream infections, surgical site infections) to mandatory reporting of local data. The European Antimicrobial Resistance Surveillance System (EARSS) is outlined above; in 2005 the European Centre for Disease Prevention and Control was established. In the USA, the Centers for Disease Control and Prevention (CDC) coordinates surveillance of antibiotic resistance via a number of programmes, including the National Nosocomial Infections Surveillance System (NNIS) with a specific subset for critical care which collects detailed information on major interventions including catheterisation. The World Health Organization provides guidance on the global response to antimicrobial resistance and is also coordinating efforts to combat specific communicable diseases. Finally, HELICS (Hospitals in Europe Link for Infection Control through Surveillance) is a pan-European surveillance system mainly evaluating ICU nosocomial infections and surgical site infections. Currently in phase IV it aims to produce routine analyses of nosocomial infection and disseminate these throughout its network and to also extend its educational programme to regions with little experience in infection control.

Surveillance systems are complex and labour-intensive. In addition to staff and laboratory facilities, they require a database to collate information, reporting mechanisms, and systems of quality assurance. In the 1970s, the US Study on the Efficacy of Nosocomial Infection Control showed that surveillance as part of infection control reduced the incidence of nosocomial infection by 32% in comparison to hospitals without the strategy where it increased by 18%. The main elements ensuring reduction were at least one epidemiologist for every 1000 beds, one specialist nurse for every 250 beds, and a surveillance system with reporting of nosocomial infection rates.

How may surveillance systems impact upon local practice?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Surveillance systems may impact upon local practice in a number of ways. Data on incidence of MDR pathogens will assist in empirical choices of antibiotics. Knowledge of resistance patterns will influence antibiotic selection and assist in the development of guidelines locally. Surveillance systems will also provide benchmarking data to assess regional effectiveness of infection control procedures.

In text References

(Haley et al. 1985; Rüden et al. 1997; Umscheid et al. 2011)

Note

Local, national and international surveillance systems provide vital information on nosocomial infections and their aetiology.

Which organisms are particular focuses for international and national surveillance systems?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Although all multi-drug resistant pathogens are of concern, particular focus at present is on MRSA, VRE and Clostridium difficile. EARSS routinely surveys MRSA, Streptococcus pneumoniae, Escherichia coli, Enterococcus faecalis, Enterococcus faecium, Klebsiella pneumoniae and Pseudomonas aeruginosa.

Surveillance includes the following elements:

- Administrative controls for medical equipment, healthcare workers and patients
- Engineering controls
- Epidemiological surveillance and intervention.

Administrative controls for medical equipment include cleaning protocols for multiple use devices and procedures for introduction of devices; for patients it includes guidelines for isolation, guidelines for admission to ICU and details of various surveillance procedures. Administrative controls for healthcare workers include training in infection control and recommendations for nurse to patient ratios. Surveillance of staff needs to include consideration of the consequences for the individual as well as their co-workers and patients. The Centers for Disease Control and Prevention supports a National Surveillance System for Health Care Workers (NaSH), with extensive guidance.

Think

During routine surveillance, a junior doctor in your ICU team is found to be a nasal carrier of MRSA. A course of topical mupiricin is ineffective. How might this problem be analysed and approached?

Engineering controls relate to adequate bed spacing, isolation facilities and adequate sink facilities on the ICUs and other aspects of unit layout and organisation. These two areas are considered in more detail in prevention of nosocomial infection and antimicrobial resistance.
Surveillance systems have a number of purposes:

- Identifying, predicting and understanding trends in resistance
- Detecting the emergence of new resistance mechanisms
- Developing, implementing and monitoring the impact of new empirical antibiotic regimens, infection control and public health guidelines
- Identifying outbreaks of resistant organisms
- Identifying the need for new antibiotics
- Identifying the need for new diagnostic tests
- Education of healthcare providers, patients and the public
- Providing data for new drug applications.

5. 1. 2. Local surveillance measures

Local surveillance involves the continuous collection, recording, analysis and feedback of data on the incidence of nosocomial infections within a ward, department and / or hospital. Each ICU should have a policy for surveillance and screening of MDR pathogens and nosocomial infections. The nature of the policy will depend on local infection rates, the prevalence of MDR pathogens in the environment and case mix. The policy should include guidance on admission screening, the frequency and escalation of routine monitoring, specific sampling techniques, eradication therapy, and isolation or cohorting. Sampling from the ICU environment may also be required.

- The aims include:
  - Detection of potential infection control problems
  - Confirmation of infection control problems
  - Causation analysis
  - Remediation
  - Monitoring remediation
- Methods of local surveillance include:
  - Total (incidence surveillance)
  - Alert organism
  - Prevalence
  - Targeted
  - Priority-directed

Total surveillance involves the routine collection of information, input into a database, analysis and dissemination of that information on the occurrence of all nosocomial infections in a specified ward or hospital. Its main drawbacks are those of cost – both in terms of microbiology resources and of staff time to collect samples routinely, and a lack of focus.
Alert organism surveillance is the term used for continuous monitoring of key organisms such as MRSA or VRE. It provides data on incidence over time and makes it easier to determine when outbreaks are occurring or endemic levels rising.
Prevalence surveillance is aimed at detection of active infections at a single point in time over a period of time. The rate is the ratio of number of affected individuals in the defined population to the number of the population at risk. It has the advantage of being easily repeatable, generating information on trends over time.
Targeted surveillance looks at very specific infections, patient groups or areas in the hospital. It is extremely focused as it requires clear definitions of the problem (e.g. ventilator-associated pneumonia, CRBSI, MRSA wound infection).

Priority-directed surveillance allocates resources by the magnitude of the problem and also sets aims for prevention which can be easily audited.
The optimal approach is probably a combined one, with different strategies for different problems. The cost–benefit of routine surveillance microbiological sampling in all patients is uncertain. Information technology may provide a useful way of disseminating information about surveillance results. Automated alerts can be used with appropriate hospital information systems, particularly for MDR pathogens that may necessitate isolation or other measures.

Think

What routine surveillance occurs in your hospital? What information do / would you like to receive from the routine surveillance programme in your ICU?

References

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5. 2. Laboratory techniques in infection control

The clinical microbiology laboratory has a crucial role in infection control. Processing of routine specimens may allow for detection of outbreaks, previously unsuspected. In addition, a policy for screening of patients, reflecting local flora and resistance patterns, will need to be formulated in collaboration with the intensive care clinicians, clinical microbiologists / infectious diseases physicians and the laboratory. Good lines of communication are also essential to allow for appropriate prioritisation of specimens.
Increasingly, laboratories are using rapid diagnostic techniques involving PCR-based technologies, which provide results more rapidly.

5. 2. 1. Microbial typing

Molecular techniques in microbial typing have revolutionised descriptive epidemiology. In order to ‘prove’ a link between cases, it is necessary to demonstrate that all the isolates in a suspected outbreak are indistinguishable by a robust typing method. It is not possible to prove that isolates are identical, only that they are indistinguishable!

Before the introduction of DNA-based techniques (genotypic), a number of approaches were taken (phenotypic); some of these may still be useful in providing preliminary data.

- Basic identification of microbial species: identification of an uncommon isolate e.g. Acinetobacter baumanii in a unit where it is not endemic, may be sufficient to suggest an outbreak. There are a number of manual and automated systems based on enzyme detection.
- Antibiotic susceptibility pattern: this may be characteristic e.g. in vancomycin-resistant Enterococcus, or different strains of MRSA, and again may be suggestive of an outbreak. Many countries have national standards on how susceptibility testing is carried out (e.g. National Committee for Clinical Laboratory Standards (NCCLS) in the USA and used widely elsewhere; British Society for Antimicrobial Chemotherapy, (BSAC)).

Genotyping is not usually carried out in a routine microbiology laboratory, but in one or more local or national reference centres. Results are therefore not available immediately and close collaboration with the infection control team will be required to manage a possible outbreak in the interim. Genotyping is most developed for bacterial species. A number of different methods exist; not all are appropriate to all microbes, and descriptive typing systems may be specific to particular microbes. Examples include:

- Polyacrylamide fluorescent gel electrophoresis (PFGE), which involves use of a restriction enzyme to cut the DNA at different points, then separation on a gel to generate a DNA ‘fingerprint’, which can be compared visually or electronically.
- Multi-locus sequence typing (MLST) in which a number of loci are sequenced and the sequences compared.

Challenge

Arrange to visit your hospital microbiology laboratory. Discuss with them which techniques are utilised to identify pathogens and which methods they would use to identify related pathogens locally.

In text References

(Versalovic and Lupski. 2002; Liesenfeld et al. 2014)

References

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5. 3. The infection control team: a multi-disciplinary approach

The control of hospital-acquired infections is a responsibility shared by all those involved in healthcare from the patient and the public to the clinical staff, ancillary staff, and management. Many hospitals have developed teams with particular interest in infection control and with focused knowledge and skills in the area. Infection control should be directly represented within the hospital management board, usually through the Infection Control Committee.

Note

Collaboration with local microbiology teams is vital to maintain awareness of antimicrobial sensitivity patterns and ensure appropriate treatment.

5. 3. 1. Goals of infection control teams

- Audit and surveillance
- Advise clinical areas on management and prevention of hospital-acquired infections (HAIs)
- Advise individuals – may require links with occupational health
- Outbreak management
- Production of guidelines for staff on prevention and management of infection
- Development of protocols for HAI control
- Involvement in research to improve infection control practice
- Liaising with non-clinical departments (e.g. catering)
- Root cause analysis.

What is root cause analysis and how may it assist in infection control?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Root cause analysis is an approach to examining how a series of preceding events or errors within a system lead to a final event. By targeting interventions at these 'root' causes, the chances of the final event re-occurring may be minimised. With respect to infection control, the final event may be the infection of a patient with an MDR pathogen and the root causes could be inadequate infection control on a ward due to staff shortage, lack of education, failure to screen the patient prior to transfer to a unit, inappropriate antibiotic treatments etc.

5. 3. 2. Members of the infection control team

Nursing staff

Nurses with particular interest, training and skills in infection control will typically have frequent contact with many ward areas and provide first point of contact for ward nurses. In most organisations they undertake education and dissemination of good practice as well as the collection of audit data. Each clinical area should identify a link nurse to improve liaison and work with the intensive care nurses.

Clinical microbiologists / infectious diseases physicians

Physicians with specialist interest and qualifications in medical microbiology provide the key link between laboratory and the clinical environment. In addition to leading the team, managing outbreaks, and providing advice on antimicrobial usage, microbiologists or infectious diseases (ID) physicians should undertake joint ward rounds with the ICU team. They have an important role in formal and informal education of hospital staff, and developing local policies.

Laboratory staff

Scientific staff process and analyse large numbers of specimens each day and will be the first to identify potential pathogens. The quality of their work is evidently central to providing a timely and reliable service.
Membership of the Infection Control Committee will be influenced by local expertise and specialist facilities. A typical committee may include

- Microbiologist / ID physician
- Surgical / medical representatives
- Patient representative
- Intensivist and / or representatives of other hospital specialist area
- Nurses representing appropriate parts of the hospital
- Others e.g. pharmacist, occupational health physician, administrator.

6. Infection control management

6. 1. Source identification

6. 1. 1. Within the patient

Identifying the source of an infection sounds simple, but in the early stages clinical features may be non-specific, while in the later stages of critical illness patients can have multiple potential infections as well as being colonised with potential pathogens. The key to successful management is early recognition of infection and sepsis, prompt cultures of potentially infected fluids, and timely physiological support and antimicrobial treatment to allow sufficient time for accurate investigation. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. The new Sepsis-3 definition highlights development of organ dysfunction, which represent sepsis. Early recognition of organ dysfunction using the SOFA-Score (> 2 points), lactate level (> 2 mmol/l) and hypotension (MAP< 65 mmHg) is defined to detect sepsis. Early detection is necessary for early treatment to reduce mortality. Therefore it is recommended that each hospital should have a performance improvement program for sepsis and sepsis screening for acutely ill, high risk patients. The new guidelines recommended a new score without use of laboratory tests to diagnose sepsis outside the intensive care unit. Quick sofa score, qSOFA, (tachypnoea, hypotension and reduction in mental status) is helpful to detect early sepsis patients with risk in normal wards, emergency room and out of hospital.

What investigations may assist in the identification of the source of sepsis in a critically ill patient?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Possible investigations may include general investigations such as full blood count, urea and electrolytes, serum amylase, liver function tests, CRP, coagulation screens and more site specific tests such as lumbar puncture, chest/ abdominal plain radiography, ultrasonography, computerised tomography (with contrast), magnetic resonance imaging, labelled white cell scans or even exploratory surgery.

Which score can help to identify sepsis patients at risk for mortality outside the intensive care unit?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Outside the intensive care unit a score without laboratory parameter resulting from simple clinical signs should help to identify patient at risk. The q-SOFA score is fulfils these requirements.

Which parameters did you know, which are used to identify patients with sepsis following SEPSIS-3 definition?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Sepsis-3 Definition requires organ failure as a result from infection. Lactate level more than 2 mmol/l or two points using SOFA Score suffice to identify septic patients with a relevant risk of death

Consider the following approach to the septic patient:

- Severity – physiological disturbance, therapeutic dependence, organ failures

- Symptoms – take a clinical history
- Signs – full clinical examination; laboratory investigations including blood
- Site – body region primarily affected
- Source – most likely organ affected, and causative organism.

For a full discussion on source control and source identification see Academy module on Sepsis and Septic Shock

Note

Source identification and control is a vital aspect of managing sepsis.

In text References

(Kollef et al. 2012; Singer et al. 2016; Shankar-Hari et al. 2016; Seymour et al. 2016)

6. 1. 2. Within the population

Identifying the index case or environmental source of outbreaks of infection requires:

- A case definition. This may be a combination of clinical and / or laboratory criteria. In general, the more precisely the case is defined, the more likely the source of infection will be discovered. Typing of micro-organisms from patients is particularly useful in ensuring that the case definition is precise. However, it may not be possible to get results of organism typing rapidly enough to contribute to a case definition.
- Knowledge of the patient risk factors for acquiring or developing infection, including the means of spread of infection.
- Collection of data from cases of infection that will include the location of the case in time and place, the presence or absence of individual patient risk factors for infection, and the presence or absence of the means of spread.
- Analysis of the data collected to identify possible sources of infection. Statistical methods are often used to control for confounding factors and to identify the most likely source(s) from a number of apparently plausible possibilities. Such analysis cannot provide definitive proof of the source of an infection. Stronger confirmation of the likely source may be obtained from intervention(s) that remove the source, limit or prevent the spread of infection, or which lead to its elimination.
- Occasionally, culture of environmental samples may be useful in identifying the source of infection.

In text References

(Snow. 1855; Coggon, Rose and Barker. 1997)

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6. 2. Colonisation versus infection

6. 2. 1. Definitions

Colonisation occurs readily in hospital environments where the colonisation pressure is high. Factors determining colonisation are the same as those promoting infection. The challenge for the clinician is distinguishing between them.

Contamination is the presence of bacteria at a site (e.g. a surgical wound) prior to multiplication taking place.

Colonisation is the presence of multiplying pathogens with no overt host response or clinical symptoms. At critical colonisation the host defences are unable to maintain the balance of organisms at colonisation. Disease tolerance for limitation of tissue damage by the host and host resistance to reduce pathogen load by host immunological response are targets, which are addressed in SEPSIS-3.

In text References

(Medzhitov, Schneider and Soares. 2012; Råberg, Graham and Read 2009; Ayres and Schneider. 2013; Singer et al. 2016)

6. 2. 2. Is this patient infected or colonised?

Infection is both a microbiological and clinical diagnosis. Infection may be suspected in the absence of microbiological evidence in patients with typical features of an infective response. Conversely, positive cultures may be obtained in patients without clinical features of infection. The problem is that some critically ill patients may mount an atypical response, while in others the systemic response may not be caused by the particular organisms isolated.

- Signs of infection may include:
  - General signs of an inflammatory response including
    - Pyrexia or hypothermia
    - Leukocytosis or leukopenia
    - Tachycardia, tachypnoea
    - Raised inflammatory markers (CRP, PCT)
  - Signs of sepsis
    - Level of lactate > 2 mmol/l
    - SOFA-Score> 2 Points
    - Biomarkers of infection: an area of active research at present.
- Specific signs relevant to infective site
  - Purulent sputum production
  - Laboratory signs as yGT in cholangitis or bacteriaemia in endocarditis
  - Localised erythema, pain, induration
  - Presence of pus, including drainage secretion
  - Morphological signs e.g. x-ray, CT.

Examples of clinical decision aids include the clinical pulmonary infection score (CPIS) for VAP and the guidelines for management of catheter-related bloodstream infections (CRBSI) published by the UK Hospital Infection Society.

In text References

(Singh et al. 2000; Loveday et al. 2014)

6. 2. 3. Should colonisation be treated?

Most nosocomial infections are endogenous infection and may be preceded by colonisation with endogenous or exogenous MDR pathogens, but not all colonising organisms will produce infection. Treatment may be directed by risk for the individual patient. Implementation of prevention strategies are necessary to avoid nosocomial infection by colonised pathogens.
Previous hospitalisation, prior antibiotic exposure, chronic illness and residence in long-term care increase carriage of MDR pathogens, but in critical care patient's local resistance data are essential to avoid unnecessary overuse of antibiotics in clinically stable patients. The concept of health care associated infections has been under constructive criticism. Breaching natural defence mechanisms (tubes, catheters, surgery) or impairing host defences (immunosuppression) predispose to infection. Some MDR pathogens are very difficult to eradicate once they colonise a patient, for example VRE and Acinetobacter. Whenever possible, the predisposing factor should be treated e.g. removing central venous catheters, enhancing nutrition.

What are the potential adverse consequences of inappropriately administering treatment for colonisation?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

The concerns of inappropriate treatment of colonisation are the selection of resistant strains of colonising pathogens and the potential side effects of antibiotic usage on the patient.

Note

Determining whether a patient is colonised or infected by a potentially pathogenic organism is an important aspect of both patient care and wider infection control.

Challenge

Locate the last twenty positive microbiology results from your unit. How many of these do you think represent colonisation? Were the patients displaying signs of infection when the samples were taken? How many were treated with antibiotics?

In text References

(Kalil et al. 2016; Torres et al. 2017)

6. 2. 4. Cohorting and isolation

There are two types of isolation employed in critical care units:

- Protective isolation – of immunocompromised or neutropenic patients to reduce the potential for opportunistic infections.
- Source isolation – of colonised or infected patients to minimise potential transmission to other patients or to staff.

The 'gold' standard is isolation of the infected / colonised patient in a single room, even though the evidence is limited. In patients colonised difficult to treat pathogens and in pathogens with high resistance in the environment, the evidence is better for contact precaution. Limited availability of space or staff often result in modified forms of isolation such as cohorting infected patients together with dedicated staff in a specific area of the ward or hospital. Cohorting has less impact on nursing dependencies than isolation but requires more vigorous enforcement of standard infection control measures than single rooms.

The benefits of isolation are that it physically restricts access to the patient, limits opportunities for spread to staff, reduces the extent of environmental contamination, and provides visual and psychological reinforcement of infection control measures, such as handwashing and donning gowns.

The adverse consequences of isolation include altered nursing allocations with the potential for increased workload in other areas, and hindering routine clinical care. Isolated patients may be neglected, suffering more preventable adverse outcomes (pressure sores, falls, fluid or electrolyte disorders, symptoms of depression, anxiety), poorer quality documentation of care, and being less satisfied with the care they receive. Single rooms can hamper mobile radiological investigations, while transport of infected patients to other areas of the hospital for investigation or treatment may be delayed to allow completion of elective work. Threat of MDR also provoked fear by nurses to be colonised themselves and particular their family.
Evidence of benefit for isolation is weak, and there is a lack of consensus on the effects. Studies are heterogenous, and subject to confounding variables, particularly in adherence to infection control measures such as hand hygiene. The setting in which isolation is applied and the background prevalence of MDR organisms will also influence results. Isolation is a package of interventions and must be evaluated in the context of the healthcare system as a whole. It will not be effective if clinical staff fail to apply best practice measures.

Think

Are there facilities for isolation on your unit? Talk to the nursing staff about the last patient isolated and enquire about the problems they may have encountered. Did you have discussions at home about colonisation of healthcare workers?

In text References

(Cepeda et al. 2005; Cooper et al. 2004; Derde et al. 2014; Cohen, Cohen and Shang 2015; Abad, Fearday and Safdar. 2010)

6. 2. 5. Requirements for isolation

Infection control teams should be involved in designing and commissioning new ICUs. Essential components include handwashing facilities at each bed space, sufficient space between beds, and air conditioning systems with the capacity to provide both negative pressure (for source isolation) and positive pressure (for protective isolation) ventilation. Every ICU should have the capacity to isolate or cohort patients, and isolation rooms should have a lobby area, tight fitting doors, and glass partitions (with integral blinds) for observation purposes and for noise reduction. Electric doors for patient transfer and small entrances for healthcare workers facilitate to keep the main door to patients room in ICU closed. This all together is helpful for implementation of hygiene strategies as well day-night rhythm for patients.
The physical facility should be accompanied by infection control policies developed collaboratively by the infection control and ICU teams. Policies should include guidance on:

- Performance and monitoring adherence to standard infection control measures
- Which MDR pathogens require patient isolation
- Which patient factors might make isolation inappropriate
- Antimicrobial prescribing
- Education and audit

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6. 3. Antimicrobial therapy

Between 25-50% of hospital inpatients receive antimicrobials and in the ICU the proportion is higher. ICU patients typically receive more potent and broadspectrum antibiotics. Patients are more likely to have MDR pathogens. Clinicians face a daily challenge in providing timely and effective antimicrobial treatment while at the same time wishing to avoid over-treatment. General approaches to optimise practice are given on the following page.

Limit unnecessary antibiotic administration:

- Develop hospital-based guidelines
- Create an antibiotic use quality-improvement team
- Provide education on antibiotic usage
- Create prescribing limitations
- Enforcing functions though computerised prescribing (e.g. limit duration)
- Move to narrow-spectrum when culture results available

Optimise antimicrobial effectiveness:

- Joint ward rounds with microbiologist/ infectious diseases consultant / attending
- Review prescriptions and laboratory results daily
- Consider antibiotic cycling / rotation

- Limit short-term prophylaxis to specific clinically validated indicators
- Consider PK/PD (pharmacokinetic and pharmacodynamics), which means dosing

In text References

(Kollef and Fraser. 2001; van Duijn et al. 2018; Rhodes et al. 2018)

6. 3. 1. Protocols and guidelines

Standardised care improves reliability and efficacy. Clinical guidelines should be evidence-based, clinician-developed, multidisciplinary, and supported by management. Electronic prescribing systems enable antimicrobial guidelines to be incorporated in the form of clinical decision support, including forcing functions to limit duration. They also allow audit, and improve patient safety by avoiding drugs to which patients may be allergic. An example would be a protocol to limit the number of doses of postoperative antibiotics following elective surgery which may be easily implemented using electronic prescribing systems.

What would be the important features of an antibiotic protocol for nosocomial infections in critical care?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

An antibiotic protocol for nosocomial infection on the ICU should include details of likely organisms, initial empirical antibiotic choice, focused therapy choice when results become available, indications for combination therapy, minimum and maximum duration of usage for all antibiotic courses and exceptions where prolonged therapy is indicated.

In text References

(Nachtigall et al. 2014; Rawson et al. 2017)

6. 3. 2. Duration and specificity of antimicrobials

Mortality is increased if antibiotics are delayed, particularly in critically ill patients, or the wrong choice is made. Common practice is therefore to start broad-spectrum antibiotic cover, targeted to the identified, most likely clinical infection where possible, until culture results allow refinement to narrow-spectrum. In clinically stable patients or patients without sepsis following SEPSIS-3 or without indication for special infectious diseases such as endocarditis calculated broad spectrum ant-iinfective treatment can wait until microbiological results are available. In patients with septic shock a delay of antiinfective treatment is a risk for mortality.

In text References

(Kollef et al. 1999; Guidry et al. 2017)

Prolonged treatment may drive resistance and other complications. Surgical prophylaxis should be restricted to one or two intra-operative doses. Short treatment courses of three days may be sufficient for some infections e.g. uncomplicated UTIs. The optimal duration of antimicrobial usage remains controversial with recommendations ranging from five to ten days. In addition, longer courses may be required for some micro-organisms (e.g. Pseudomonas, Acinetobacter, MRSA, H5N1 influenza), or for infection in inaccessible or poorly penetrated sites (e.g. pancreas, nervous system, heart valves).

Note

Inadequate antimicrobial therapy is a risk factor for mortality in severe sepsis.

In text References

(Singh et al. 2000; Scottish Intercollegiate Guidelines 2000; Kumar et al. 2010; Hranjec et al. 2012; Sánchez et al. 2017)

6. 3. 3. Restricted formularies

Antibiotic prescribing may be restricted by clinical area, speciality, or seniority. Restrictions may be applied to classes of drugs that have broad spectrums (e.g. carbapenems), those associated with rapid emergence of infection (cephalosporins) and those associated with toxicity (e.g. aminoglycosides). Evidence of efficacy of this strategy is limited. It may reduce unnecessary expenditure, and may be useful in controlling outbreaks. Mortality increased rapidly in patients with shock, therefore in ICUs restriction order should not cause of delay of necessary effective antibiotics e.g. MDR infections.

6. 3. 4. Antibiotic rotation

Antibiotic class cycling (antibiotic rotation) involves the withdrawal of a class of antibiotics for a period of time, followed by reintroduction of that class, thereby reducing the selection pressure of resistance to an agent. The rotation can be used on an individual unit basis, between wards within a hospital or at the level of the whole institution. It is suitable only for bacteria for which there is a selection of available antimicrobials. Evidence of benefit is limited. There are open questions for these strategies: Duration of rotation cyclus or of cycling cyclus is an unresolved question. New data did not show results for recommendation.

6. 3. 5. Combination therapy

An alternative to initial single agent broad-spectrum empirical therapy is a combination of single narrower-spectrum agents, on the basis that this is less likely to produce resistance and may demonstrate synergy. There is clinical evidence to use combination therapy in patients with septic shock or organ dysfunction support this recommend and in infected patients with MDR.

In what circumstances may combination therapy be useful?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Combination therapy may be useful empirically where a single antimicrobial may not adequately cover all potential micro-organisms. An example of this would be CRBSI where resistant Gram-positive and / or Gram-negative species may be the infecting bacteria and a combination of glycopeptides and a carbapenem may be an appropriate choice. The other area of usage is in the treatment of Pseudomonas sp. where some consider combination therapy reduces the emergence of resistance. Evidence for this is limited.

In text References

(Kumar et al. 2010; Qureshi et al. 2012)

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6. 4. Infectious diseases / clinical microbiology consultation

A number of studies have shown that involvement of an infectious diseases specialist in the treatment of infected patients reduces the likelihood of inadequate antimicrobial treatment. The impact of this intervention will clearly depend on the sophistication of the primary teams, their adherence to protocols, and the availability of laboratory results. Joint ward rounds with clinical microbiologists improve the reliability and timeliness of care and provide important opportunities for refining therapy and for education.

Challenge

Perform an audit of antibiotic prescriptions in your unit. What proportion of prescriptions follow the unit antibiotic protocol for antimicrobial choice and duration?

In text References

(Honda et al. 2010)

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7. Prevention of nosocomial infection and antimicrobial resistance

There are various strategies that may be employed to minimise the occurrence of nosocomial infections and the emergence and spread of multidrug resistant pathogens in the critical care environment. Preventative measures may be divided into three broad categories: those targeted at the general environment which attempt to minimise horizontal transmission of pathogens; those targeted at preventing specific nosocomial infections; and those targeted at preventing selection of MDR pathogens in general.

- General (environmental) preventative measures
    - Handwashing and alcohol rub disinfection
    - Gowning / barrier methods
    - Cleaning environment
    - Architecture of unit / unit layout
    - Isolation / cohorting
    - Workload of ICU
- Specific (patient-related) preventative measures
    - Aseptic techniques
    - Appropriate use of prophylactic antibiotics
    - Reduction in ventilator-associated pneumonia
    - Reduction in catheter-related bloodstream infection
    - Use of care bundles
    - Selective decontamination of the digestive tract (SDD)
- Reduction in selection of MDR pathogens
    - Antibiotic policy
    - Infection control consultants and team
    - Source removal
    - Antibiotic rotation
    - Eradication therapy

7. 1. General (environmental) preventative

Horizontal transmission from healthcare environment to patient can occur in the ICU as in the rest of the hospital. The extent to which this causes nosocomial infection in the ICU is still uncertain, but few would deny its probable importance. Some research suggests that colonisation before ICU admission is more contributory.

What factors should reduce or prevent horizontal transmission in your ICU?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Factors reducing horizontal transmission on the ICU include:

- Handwashing / hand hygiene
- Gowning / barrier methods
- Cleaning the environment
- Architecture of unit / unit layout
- Isolation / cohorting if infection occurs
- Workload on ICU.

In text References

(Stiller et al. 2016; Kola et al. 2010)

7. 1. 1. Factors related to hand hygiene

Hand hygiene is considered a key element in the prevention of horizontal transmission of pathogens between patients and was the first international challenge supported by the World Health Organization's World Alliance for Patient Safety.
There is a large body of research demonstrating that clinicians' compliance with hand hygiene protocols is poor, and that we lack insight into the true extent of non-compliance. Doctors are worse than nurses, and neither are as compliant as relatives. While these process failures are unquestioned, it is more difficult to establish definitive proof that improving compliance has a beneficial impact on outcomes in terms of reducing nosocomial infection rates. Pittet et al. showed that a hospital-wide programme to improve compliance was associated with a progressive reduction in MRSA attack rates, but compliance amongst doctors at the end of the six-year study was only around 20%.

What factors reduce the compliance with hand hygiene protocols?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Commonly cited associations and reasons for poor compliance include lack of education, awareness and insight; male gender; excessive workload and suboptimal nurse: patient ratios; poor handwashing techniques; inadequate facilities such as too few hand-basins or non-availability of alcohol hand-rub; skin irritation from antiseptics; and lack of belief that hand hygiene is responsible for transmitting HAI.

Challenge

Take the opportunity during ward rounds to observe the following:
(i) How many staff–patient contacts there are, and how many were accompanied by appropriate hand hygiene and protection measures?
(ii) How often do staff wearing disposable gloves touch themselves or objects in the patient's environment and then touch the patient?
(iii) How long does it take to wash one's hands compared with applying alcohol hand rub? Estimate the amount of time a nurse would spend on hand hygiene during one shift.

In text References

(Lydon et al. 2017; Gould et al. 2017; Pittet et al. 2000)

7. 1. 2. Barrier precautions: gloves, gowns and masks

The use of gowns and gloves as a barrier method reduces the colonisation of the healthcare worker and the transmission of pathogens already colonising the staff member. Up to 65% of healthcare workers will contaminate their clothes when routinely caring for patients with MDR pathogens such as MRSA. In addition, it has been shown that in up to 25% of cases, a healthcare worker's hands can become re-contaminated with pathogens after contact with contaminated clothing. Studies have evaluated the addition of gowns (disposable aprons) to gloves alone as a method and the majority show a benefit. There is no evidence that the use by staff of standard surgical face masks protects the patient. N95 masks provide protection for staff against droplet contamination during aerosolising procedures.

Note

Norovirus (Norwalk-like virus) is the commonest viral cause for gastroenteritis. Its ready transmission and durability in the environment make outbreaks in institutions more common.

7. 1. 3. Isolation / cohorting

Isolation and cohorting are dealt with earlier in this module.

7. 1. 4. The environment

Cleanliness

Some pathogens can survive for long periods in the environment, particularly MRSA, VRE, Acinetobacter sp., Clostridium difficile and norovirus. MRSA has been found on keyboards, taps / faucets, curtains and other similar surfaces.
In isolation rooms, studies have shown the presence of MRSA around infected or colonised patients in the bed material, in the air and on various surfaces within the room. High-quality cleaning is an important component in encouraging staff to take pride in their workplace, and hence in their work; and domestic staff should be valued as members of the ICU team.

7. 1. 5. Architecture and layout

Infection control is central to the design of a new ICU. Points for consideration include:

- Provision of single isolation rooms with negative and positive pressure ventilation
- Adequate space around beds – ideally 2.5 to 3 metres apart
- Adequate isolation facility in the unit
- Services (electricity, gases, vacuum) sited to allow all-round access to the bed
- Minimum of one large wash basin for every two contiguous beds, with elbow-operated mixer taps
- Alcohol gel dispensers at entry, exits, every bed space and every work station
- Adequate storage space for equipment
- Separation of clean and dirty utilities
- Hard, moveable partitions between beds to provide privacy and permit cleaning
- Provision of a stethoscope for each bed, adequate sharps disposal
- Easy to clean portable monitoring and ventilators
- Sterile procedure trolleys (‘carts’)
- Sterile supplies and stock-taking
- Routes of ‘traffic flow’ through the ICU.

Challenge

Map out a plan of your intensive care unit. Note on the plan the location of the above features. How compliant would your unit be to these standards? How would you choose to improve the layout of the unit?

7. 1. 6. Staff workload

There is some evidence that ICU workload may affect patient outcomes in a number of ways relevant to nosocomial infections. Nursing shortages may increase workload and decrease compliance with basic infection control measures. Shortage of staff may prolong the weaning process and render the patient more susceptible to VAP. Work in both adult and neonatal ICU identifies understaffing and poor nurse-to-patient ratios as a risk factor for nosocomial infections. In particular this appears to be related to increased CRBSI rates in adult surgical critical care.

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7. 2. Specific (patient-related) preventative measures

In addition to general measures to reduce the spread of nosocomial infection there are several strategies focused on specific nosocomial infections in critically ill patients. Of these, ventilator-associated pneumonia and catheter-related bloodstream infections are amongst the most important.

7. 2. 1. Reduction in ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most frequent ICU-acquired infection. VAP affects up to 50% of such patients, with an acquisition rate of 3% per day for the first week, 2% per day for the second, and 1% thereafter. It prolongs ICU stay and increases relative mortality risk by around 25% and attributable mortality of about 3-10%. Differences in mortality might be influenced by false positive diagnosis up to 20-30% of VAP patients. The diagnosis requires a combination of clinical and microbiological data. The “low” attributed mortality requires a high number of patients in randomised trials to demonstrate reduction in mortality resulting from prevention strategies. The guidelines recommend to re-evaluation of pneumonia diagnosis after 72 hours. Likelihood of infection can be estimated using the Clinical Pulmonary Infection Score (see table 1), even though CPIS is not recommended by the guideline for diagnosis of pneumonia. In children a similar combination of clinical score and microbiological data has been proposed.

Table 1: Clinical pulmonary infection score for ventilator-associated pneumonia

CPIS Points	0	1	2
Tracheal Secretions	Rare	Abundant	Abundant and Purulent
Chest X-Ray Infiltrates	No Infiltrate	Diffused	Localized
Temperature ℃	≥36.5℃ and ≤38.4℃	≥38.5℃ and ≤38.9℃	≥39℃ or ≤36℃
Leukocyte Count, per mm³	≥4000 and ≤11000	<4000 or ≥11000	<4000 or >11000 and band forms ≥500
PaO2/FiO2 mmHg	>240 or ARDS		≤240 or No Evidence of ARDS
Microbiology	Negative		Positive

- Adapted from Kalanuria AA, Zai W, Mirski M. Ventilator-associated pneumonia in the ICU. Critical Care 2014;18(2):208

We differentiate between intrinsic and extrinsic infection. Pathogens from gastro-oesophageal and / or the oropharyngeal tract reach the trachea and pass the cuff resulting in micro-aspiration (intrinsic infection). Pathogens of the patient's environment reach patients lower airways e.g. by inadequate hand hygiene or non-sterile suctioning catheter.

Table 2: Mechanism of VAP

Intrinsic infections	Extrinsic infection
• Regurgitation and microaspiration of pathogens from colonised gastric fluid • Micro-aspiration of pathogens from oropharyngeal area	• Opening an disconnection of tube • Opening of ventilator circuits • Inadequate tracheal suctioning • Insufficient hand hygiene

Tolerance of a tracheal tube in mechanical ventilated patients usually needs targeted analgesia with opiods and/or sedatives and reduce coughing and swallowing, parts of the natural host defense against micro-aspiration.

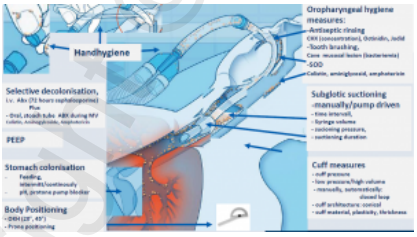

Figure 3: VAP- prevention measures. Adapted from http://www.krankenhausinfektionen.info/ki-de/kischulungsmaterialien, praesentation-atemwegsinfektionen.pdf, approved by bvmed.de

In text References

(Klompas 2007; Langley and Bradley. 2005; Kalil et al. 2016; Bekaert et al. 2011; Dalhoff et al. 2012; DAS-Taskforce et al. 2015; Musher 2008)

Avoiding intubation

As intubation and mechanical ventilation are significant risk factors, non-invasive ventilation may reduce VAP rates. However, this must be balanced against the increased risk of VAP from failed trials of extubation and re-intubation. Interventions which promote earlier liberation of the patient from the ventilator may also reduce exposure to risk of infection; this includes targeted sedation protocols coupled with weaning protocols and inclusive daily assessment of readiness of extubation using spontaneous breathing trails (SBT).

Early Tracheostomy

Tracheostomy might be effective to produce better endotracheal tube tolerance resulting in reduction of analgetics and sedatives and might maintain host defense. The last meta-analyses concluded that early tracheostomy was not efficient in preventing VAP, with no benefit on any associated outcome except sedation reduction.

Aspiration of subglottic secretions

Pooling of secretions around the cuff leads to micro-aspiration, main mechanism of VAP. First the mechanism of micro-aspiration and VAP should convince us of subglottic drainage usage. Endotracheal tubes with a subglottic suction port reduce VAP and length of stay in ICU, but did not reduce mortality in prospective studies. We can do subglottic aspiration manually by syringe e.g. hourly or using an electric pump in use of special tubes. Aspects about the amount and quality of tracheal secretion (purulent/aqueous mucus) as well as technical aspects (duration of suctioning, level of suctioning, interval of suctioning) up to now are not well investigated in clinical setting. But on the other side mucosal trauma has been reported.

Continuous control of endotracheal cuff pressure

Continuous control of cuff pressure should reduce micro-aspiration and tracheal mucosa lesions by high cuff pressure. Continuous cuff control might be helpful in combination with subglottic drainage and might reduce risk of VAP. No reduction of duration of mechanical ventilation, nor reduction of ICU length of stay or mortality has been reported by use of continuous cuff control. Cuff control is a convincing concept, but further studies are necessary.

Semi-recumbent body positioning and early mobilisation

Positioning patients at 45 degrees to the horizontal had been demonstrated to reduce passive regurgitation and VAP. Recent evidence suggests this may be difficult to achieve and that the benefit may be less than initially claimed. Early physical treatment, semi-recumbent body positioning, targeted sedation and weaning protocol are part of a concept of a awake, mobilised active ICU patient without anxiety.

Enteral feeding

Enteral feeding can contribute to VAP by neutralising the pH of the gastric contents and promoting bacterial growth, as well as increasing regurgitation. However, alternative routes or regimens have not altered outcome.

Stress ulcer prophylaxis

Both H2 antagonists and antacids have been identified as independent risk factors for VAP. These agents are not recommended for patients at low risk of bleeding and particularly enteral feeding.

Selective decontamination of the digestive tract

The rationale behind selective decontamination of the digestive tract (SDD) is that colonisation of the GI tract with potentially pathogenic Gram-negative micro-organisms causes VAP by direct translocation from gut to oropharynx. The technique consists of short-term systemic antimicrobials (usually a cephalosporin) to eradicate community-acquired infection, and longer-term topical (oropharyngeal and enteral) non-absorbable antimicrobials including polymyxin, tobramycin and amphotericin. The principle is to abolish pathogenic microorganisms while preserving the normal colonic Gram-negative anaerobes, Bacteroides sp.

Since its introduction in 1981, more than 56 randomised studies have been conducted in around 10,000 patients. Twelve meta-analyses have been performed, which demonstrate significant reductions in mortality and in infectious morbidity without promoting emergence of resistant organisms. Moreover a reduction of ICU length of stay and of duration of mechanical ventilation is not consistent to reduction of mortality in SDD studies. Concerns persist about stimulating emergence of Gram-positive resistance with this technique, but the evidence suggests that SDD is associated with less resistance than conventional use of systemic antimicrobial agents. SDD studies have been performed in countries with low prevalence of MRE. On the other side in SDD studies, reduction in use of systemic anti-infectives is reported. Harm in SDD in countries with high prevalence of MRE is under discussion and we wait for results of a European SDD study.

SOD

Oropharyngeal decontamination with antiseptics (chlorhexidine, Jodid, Octinidol) is part of VAP bundle in a high number of hospitals. Chlorhexidine in different concentrations is mostly used in clinical practise. Limited efficacy in Gram-negative pathogens, possible side effects by micro-aspiration of chlorhexidine and some evidence that mortality might increase in use of chlorhexidine, should be considered.

Note

Many of the factors affecting the incidence of VAP are not easily modifiable. Stress ulcer prophylaxis and enteral nutrition are necessary risks. In a meta-analysis only SDD reduced mortality, but altogether of all different intervention for VAP prevention a reduction in mortality can be observed. This might underscore a VAP bundle might be effective.

Think

If you were critically ill and undergoing controlled mechanical ventilation, which of the interventions listed above would you want used in your care?

What aspects of early versus late tracheostomy may reduce the incidence of VAP?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

The potential benefit of early tracheostomy on VAP is the facilitation of sedative withdrawal, improved cough reflex, improved patient mobility and shorter duration of ventilation. Prevention of VAP is not well documented.

In text References

(Girard et al. 2010; Liberati et al. 2009; Carron et al. 2013; Caroff et al. 2016; Schweickert et al. 2009; Mao et al. 2016; Suys et al. 2013; American Thoracic and Infectious Diseases Society of. 2005; Babcock et al. 2004; Roquilly et al. 2015)

7. 2. 2. Reduction in catheter-related bloodstream

Catheter-related bloodstream infections (CRBSIs) are an important nosocomial infection in the ICU. The CDC estimates a median rate of 1.8 to 5.2 bloodstream infections per 1000 catheter days, and it is likely that these cause a substantial number of deaths amongst hospitalised patients each year. CRBSI are associated with a high mortality and long term burden. CRBSI are not only related to CVCs but also to arterial catheters (AC) and peripheral venous catheters (PVC) – despite the low incidence of PVC related BSI, their higher frequent use promote a high quantity of infections, which has been showed in a prospective study
Evidence-based interventions to reduce CRBSI include:

Avoiding the femoral route for routine cannulation

The incidence of CRBSI is lower with subclavian CVCs versus femoral CVCs.

How may the differing anatomical locations for CVC insertion influence the occurrence of CRBSI?

COMPLETE TASK THEN CLICK TO REVEAL THE ANSWER

Evidence suggests the optimal site for CVC insertion is the subclavian route with regard to the incidence of CRBSI. However, the risk of mechanical complications is higher in this area and must be taken into account. Femoral lines have a high incidence of CRBSI due to both the local environment in the groin and the higher incidence of thrombus formation in femoral CVCs. Internal jugular CVCs may be exposed to oral flora from secretions running onto the insertion site.

Tunnelling catheters

Evidence supports the use of tunnelled CVCs for longer-term vascular access. For shorter term access such as on the ICU, the evidence is less definite and benefit varies between studies and sites of CVC insertion. This finding does not apply to paediatrics. No significant difference has been found between longterm femoral and internal jugular catheters in some studies.

Antimicrobial catheters

Catheters may be impregnated with minocycline-rifampicin or silver sulfadiazinechlorhexidine. They are recommended for longer-term cannulation, in high-risk patients and for reduction in CRBSI rates when other methods of infection control have been maximised. Some studies indicate minocycline-rifampicin impregnation was much more effective and long-lasting (more than three weeks) in prevention of infection than silver sulfadiazine impregnated. The primary concern in relation to their broad introduction to clinical practice is not cost but the potential to drive multi-drug antimicrobial resistance.

Aseptic technique
Migration of bacteria from the skin insertion site along the subcutaneous tract is the most common route of infection, followed by contamination and colonisation of the catheter hub via exogenous sources.

- Meticulous hand hygiene and maximal barrier precautions (gloves, gown, large drapes) reduce the incidence of CRBSI when compared with more basic precautions (e.g. just gloves and a small drape)
- Chlorhexidine 2% is a more effective skin antiseptic than povidone-iodine
- The assisting nurse should be empowered to stop unsafe practice.

Use of ultrasound

Ultrasound may reduce complication rates such as misplacement and haematoma, and could therefore reduce subsequent infection. If used during catheter insertion, proper maximum barrier precautions must be taken to prevent contamination of the skin site including a sterile cover for the probe and cable and the use of sterile gel.

Post-insertion care

CRBSI can be reduced by minimising handling, proper care of connections and taps, and reducing catheter manipulation or movement. Specialised CVC nursing teams with sole responsibility for CVCs contribute to reduced CRBSI and to medical and nursing staff education. The importance of catheter hub care is noted in a number of reviews. CVC hubs with antiseptic chamber and other modifications have been reported.

Removal of CVCs

Guidelines do not recommend routine replacement of CVCs to prevent CRBSI. However, the probability of colonisation and infection increases with time, particularly after 5-7 days, so CVCs should always be removed at the earliest opportunity. A daily review and documentation of the indication of the inserted CVC is recommended and might reduce the duration of insertion, which is one of the risk factors for CRBSI. Guide wire exchanges are not recommended and should not be performed for CRBSI or for catheter-related insertion site infections. If CVCs are inserted under unsterile circumstances, their exchange should be performed as soon as possible.

Parenteral feeding

The risk of CRBSI increases when a CVC lumen is utilised for parenteral nutrition. Meticulous infection control procedures must be undertaken when handling catheter connections, and one lumen should be dedicated to total parenteral nutrition.

Reduction of false positive blood-culture samples

False positive blood cultures should be avoided because of their potential misleading consequences and harm to the patient like antimicrobial therapy and resulting costs for the health care system and real BSI Microbes with low pathogenecity proven in a single BC sample might be a hint for a contamination, whereas the detection of staphylococci, gram negative enterobacteriaceae and candida should always be taken as a serious infection even if only reported in one BC sample. The immunocompetency of the patient has to be taken into account. Garcia et al. published a systematic investigation about the best practice of blood culture sampling. The IDSA recommends the blood culture sampling out of inserted CVCs in terms of suspicious CRBSI simultaneously with two pairs of BC out of a peripheral vein. An approach to minimise BCC could be achieved with:

- Antiseptic approach before blood culture sampling (desinfection of the sampling site, hands, sterile gloves, mask)
- Alcohol disinfection of the sample bottle rubber diaphragm
- Number of samples and volume of blood
- CRBSI: send in the tip of the catheter
- BC -kits, -teams, education and teaching of BC sampling technique
- Time to incubate < 12h

A six-step strategy combining several of these elements has been shown to reduce CRBSI effectively to zero:

- Antiseptic handwashing including alcohol rub disinfection
- Full aseptic precautions
- Chlorhexidine 2% skin preparation
- Avoid the femoral route
- Minimise duration of placement
- Empower the nurse to stop unsafe practice.

Note

The key aspects of reducing CRBSI are strict aseptic technique on insertion and daily review of the need for the CVC.

The use of prophylactic antibiotics to prevent CRBSI and nosocomial infections at other sites is generally not advised. Concern exists that use of prophylactic antibiotics routinely on ICU, for example prior to intubation or re-intubation, will promote antibiotic resistance rather than just reducing the incidence of nosocomial infection.

In text References

(Cassini et al. 2016; Pronovost et al. 2006; Bates, Goldman and Lee. 1991; Alahmadi et al. 2011; Garcia et al. 2015; Stuart et al. 2013; Lamperti et al. 2012; Climo et al. 2013; Lucet et al. 2010)

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7. 3. Reduction in selection of MDR pathogens

Reduction in the selection of multi-drug resistant pathogens primarily results from effective infection control policies and effective antibiotic usage. See Factors accounting for variations in MDR micro-organisms.

8. Common Viral Infections on ICU

During routine monitoring in the early 80s only a rate of 5% of all nosocomial infections were attributed to viruses. However, availability of molecular diagnostic assays (such as RT-PCR) increased the ability to detect respiratory virus infections. Subsequently up to 23% of severe nosocomial pneumonia in adults can be attributed to viral infections. Patients with severe viral infections are frequently hospitalised in the ICU. Most respiratory virus infections are highly contagious and spread rapidly via droplet, airborne or contact. As the aetiology of disease is mostly unknown at the time of ICU admission, the possibility of a viral infection should be considered, at least in immunocompromised patients. The situation is more challenging as not every immunocompetent infected individual present typical clinical disease symptoms. Therefore, the virus can easily be cross-transmitted between patients and health care workers and vice versa. To avoid any outbreak, the knowledge of transmission routes as well as strict adherence to hospital standard operating procedures is of utmost importance.

8. 1. Viral Respiratory Infections

8. 1. 1. Respiratory syncytial virus (RSV)

RSV is a single stranded RNA virus of the family Paramyxoviridae. RSV is the most common cause of pneumonia and bronchiolitis in infants. Apart children aged from 1 to 4 years, patients older than 75 years and patients with compromised immune status are at increased risk of being affected. Over 50% of the infections were reported being acquired nosocomial and among transplant patients, the mortality rate was 20 to 100%.

Transmission mainly occurs via inoculation of the eye and nose and by indirect inoculation of large droplets after touching contaminated fomites. RSV in secretions remains viable in the environment for 6 to 12h on fomites (be aware:on gloves up to 2h and hands up to 1h). However, during coughing or sneezing small particles aerosols may travel more than 1.8m.

Key essentials to control infection spreading are education, hand washing, consistent use of masks, gowns and gloves, wearing eye protection, isolation or cohorting patients, restriction of visitors and cohort nursing and rapid RSV screening. Moreover, palivizumab a humanized mouse IgG monoclonal antibody was described to control outbreaks in neonatal intensive care units. In immunocompromised patients aerosolized ribavirin was reported being beneficial.

8. 1. 2. Influenza

Influenza is an RNA virus from the family orthomyxoviridae and is divided in three subtypes (A, B, C). While influenza A and B cause seasonal epidemics, C generally causes mild disease. Influenza A is further classified into two subtypes on the basis of the antigen properties of their two surface glycoproteins, haemagglutinin and neuraminidase. Pandemics result from the genetic reassortment (antigenic shift) in influenza A virus. Nosocomial influenza infection occurs during the annual epidemics, as incoming patients and health care workers provide a continuous reservoir. Viral shedding usually starts within the first 24 hours following inoculation (before clinical symptoms appear), reaches a peak on the second day and usually declines rapidly thereafter. Although virus is usually after inoculation not longer than 10 days detectable, continued shedding was documented in children and immunocompromised adults.

Transmission occurs via droplets, aerosol and contract transmission. During coughing or sneezing, infected individuals expel infectious particles with different sizes. While droplets (> 5µm) can be either inhaled and deposited in the upper respiratory tract or set quickly in the environment. Fine particles (< 5µM) are able to remain airborne for minutes to hours. By inhaling, deposition is in the upper but also in the lower respiratory tract possible. Finally contact transmission can occur especially as the virus remains infectious for up to 48h on non-porus surfaces.

Isolation in a single room with negative airway pressure is highly recommended. Cohorting may also be used if large numbers of patients are infected by the same influenza subtype. In addition to standard precautions, the CDC recommends implementation of droplet precautions to prevent health care associated influenza. The WHO and the CDC recommend the use of a surgical mask when caring for a patient with influenza. Respirators (FFP2/N95 or powered air purifying respirators) are highly recommended during aerosol-generating procedures. Data suggests that the use of surgical masks can prevent most influenza transmission events if appropriate air exchange, hand hygiene practices and previous vaccination is conducted. Nevertheless, apart from aerosolising procedures respirators should be worn during any influenza pandemic when population immunity is low. Vaccination for health care workers is highly recommended and improved vaccination rates significantly decreased health care associated influence among patients and personnel. Chemoprophylaxis should be considered for unvaccinated health care workers or when vaccine is likely to be ineffective. Chemoprophylaxis for hospitalised patients who were in close contact of hospitalised influenza-infected patients showed benefit in reducing transmission. Symptomatic high-risk patients and patients with respiratory failure should be treated with oseltamivir, a neuraminidase inhibitor available by mouth, to reduce the length of symptom presence.

8. 1. 3. Corona virus

Human coronavirus is a single-stranded RNA virus and was known to cause mild respiratory infections. In 2002, a novel coronavirus causing serve acute respiratory syndrome (SARS) with a 9.6% mortality was identified. Thereafter, no additional cases were reported. In 2012, the middle east respiratory syndrome (MERS) was identified in Arabian Peninsula . Subsequently, several nosocomial MERS outbreaks were reported in 27 countries. Transmission of Mers-CoV mainly occurs through environmental contamination by large droplets, contact and aerosols. Hospitalised patients with MERS-CoV should be isolated, airborne precautions and eye protection are apart from the standard hygiene procedures essential to avoid nosocomial transmission.

8. 1. 4. Adenovirus

Adenoviruses are double stranded non-enveloped DNA viruses which can cause respiratory, gastrointestinal, neurological and eye infections. Health-care-associated outbreaks of respiratory tract infections have been reported in various settings. More than 50 immunologically distinct types were detected. Adenoviruses are remarkably stable in the hostile environment and can survive for up to 49 days on nonporous surfaces. Droplet and contact precautions in addition to standard precautions and isolation are highly recommended.

8. 2. Gastrointestinal Viruses

Up to 90% of ICU patient populations are affected by diarrhoea. Several viruses can cause gastrointestinal infections. However, norovirus and rotavirus were frequently reported to cause community as well as health care based outbreaks.

Norovirus is a single-stranded positive-sense RNA virus and a member of the calicivirus group. Outbreaks have been reported in paediatric and adult ICUs. Major mode of transmission is person to person by faecal or vomitus-oral route. Rapid secondary spread to health care workers, low infectious doses, very short incubation time and survival in body excreta necessitate rapid control strategies to prevent an explosive outbreak. Measures to prevent the spread should be aggressive and focus on the identification and isolation of infected patients. Face masks are highly recommended, as aerosolising was approved being a reasonable mode of transmission. The Norovirus is highly resistant to standard disinfections. Bleach solutions of hydrogen peroxide based disinfections must be used. Hand hygiene is of tremendous importance. In addition to careful washing with soap, the WHO recommends hand disinfection with an alcohol based formulation with a minimum of 60% (v/v) concentration.

Rotavirus is a non-enveloped virus with a double-stranded, segmented RNA genome and a member of the reoviridae. Rotavirus is the leading cause of viral gastroenteritis in infants and young children and rarely affects adults. Up to 94% of hospital acquired infections diarrhoea cases in children were due to viruses and rotavirus causes 31-87% of these cases. Affected infants excrete 108-1011 virions/gm faeces which can occur prior to symptoms with prolonged shedding during re-convalescence. Rotavirus is highly transmissible at low doses and can survive for extended periods. All patients should be care with contact precautions. Rotavirus is inactivated by >40% alcohols, free chlorine >20,000ppm, > 10,000ppm iodine, phenol based compounds and calcium chelators.

In text References

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9. Conclusion

Nosocomial infection particularly due to multi-drug resistant pathogens is a key issue on intensive care units internationally. Adequate knowledge of factors increasing resistance and of factors facilitating spread of resistant microorganisms assists the intensivist in reducing this problem. Intensivists may impact upon the incidence of nosocomial infections by attention to their units and their individual practice and also at institutional level.

10. Abbreviations

1. **CNS:** Coagulase-negative staphylococci
2. **CPIS:** Clinical Pulmonary Infection Score
3. **CRBSI:** Catheter-related bloodstream infection
4. **CRP:** C-reactive protein
5. **CVC:** Central venous catheter
6. **ESBL:** Extended spectrum β-lactamase
7. **HAI:** Hospital-acquired infection
8. **ICP:** Intracranial pressure
9. **ICU:** Intensive care unit (intensive treatment unit, critical care unit)
10. **IJV:** Internal jugular vein
11. **MDR:** Multi-drug resistant
12. **MRSA:** Methicillin-resistant Staphylococcus aureus
13. **PAFC:** Pulmonary artery flotation catheter
14. **PCT:** Pro-calcitonin
15. **PPM:** Potentially pathogenic micro-organisms
16. **SDD:** Selective decontamination of the digestive tract
17. **SSI:** Surgical site infection
18. **SVC:** Superior vena cava
19. **UTI:** Urinary tract infection
20. **VAP:** Ventilator-associated pneumonia
21. **VRE:** Vancomycin-resistant enterococci

11. Glossary

- Attack rate is the incidence of infection over time, defined as the ratio of affected persons to total exposed population. It is measured from the beginning to end of an outbreak.
- Incidence is the number of new cases of a disease during a given time interval.
- Outbreak a cluster of cases of a disease linked in time and / or place.
- Prevalence is the total number of cases of the disease in the population at a given time.
- Prevalence rate is the number of current cases per population at risk.