Antibiotic resistance in the intensive care unit

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The use of antibiotics is unique in medical practice in that the treatment given to an individual may have consequence for the wider population. Pathogens may be intrinsically resistant to antibiotics, but the problem of induced or evolving resistance should not be underestimated. Increasingly, it is recognized that the use of broad-spectrum agents, even when appropriate, is a significant factor in the development of resistance in bacteria and fungi. This has major implications for healthcare in general, and particularly in the ICU where resistant organisms can present major challenges, as patients tend to be debilitated and particularly susceptible to nosocomial infection. Such infections often lead to prolonged ICU and hospital stay, and consequent increased healthcare costs.

There is a degree of inevitability to the development of antibiotic resistance. However, strategies have been proposed and evaluated that attempt to limit the development of antimicrobial resistance, maintain the usefulness of existing antimicrobials, and influence the development of novel agents. Much of what follows relates to bacterial resistance and pathogens selected by antibiotic use.

Molecular genetics of antibiotic resistance

Analysis of bacteria collected before widespread introduction of antibiotics reveals, excluding intrinsic, almost complete sensitivity. Organisms with intrinsic resistance are often of low virulence but do become a problem in vulnerable patients managed in selection pressure environments (Pseudomonas sp., Acinetobacter).

Acquisition is based on the mechanisms of genetic mutation and inter-cell transfer. Mutation is often disadvantageous to the bacteria but will, infrequently, affect antibiotic resistance. However, the transfer of resistance between bacteria is of greater importance, the mechanisms of which are not mutually exclusive:

1. Naked DNA (transformation)
   Naked DNA is released from killed bacteria and as such is common in the ICU patient on antibiotics. DNA in this form is unprotected and is quickly degraded. Bacteria have a varying ability to take up this DNA. Transformation is the process where this DNA is incorporated into the genome of another bacterium.

2. Bacteriophages (transduction)
   These are viruses that infect bacteria. A protein coat protects the DNA within and the virus relies on the bacteria’s cellular machinery to propagate it. The DNA within the virus may be exchanged or transferred to the host, and through this mechanism can transfer genetic information encoding resistance. This is known as transduction. Bacteria vary in their

Key points

- Gene transfer is the predominant mechanism of acquisition of resistance.
- The use of broad-spectrum agents is a significant factor in the development of resistance in bacteria and fungi.
- The risk of acquiring infection with antibiotic resistant organisms is positively correlated with increasing age, illness severity, debility, and length of ICU stay.
- No single measure can be effective in the prevention of infection due to antibiotic resistant organisms or in the reduction of resistance.
- Knowledge of the mechanism of transmission of resistance enables targeted efforts to control outbreaks.

The success or failure of antimicrobial treatment depends on many things, including the vulnerability of the host, the virulence of the organism, and the use of the appropriate antimicrobial (sensitivity, tissue penetration), and other clinical interventions (removal of foreign bodies, devitalized tissue, drainage of abscesses). There is a tension between ensuring prompt treatment of infection, which unless the cause is obvious requires the use of broad-spectrum agents and the risks associated with a poorer outcome from delayed or inappropriate treatment.

Bugs, drugs, and the patient

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susceptibility to infection with bacteriophages; *Corynebacterium diptheriae* and *Vibrio cholerae* are examples of bacteria that commonly receive genetic information through this route.

3. **Plasmids (conjugation)**

These are self-replicating circles of DNA that exist within the bacteria but are separate from the chromosome. They lack the protective coat of the bacteriophage and are unable to move independently of the bacteria. Despite these limitations, they are the most important routes of transmission of genetic information within the intensive care unit.

4. **Transposons**

These are small segments of DNA that can encode resistance genes. They also encode for their mobility, thus allowing them to move from plasmid to plasmid, or within the main genotype. As such they can transmit resistance between cells.

**Mechanisms**

Different mechanisms of antibiotic resistance have been described in bacteria. These include enzymatic inhibition, decreased permeability, antibiotic efflux, target modification (ribosomes, cell walls, enzymes), and development of alternative targets or pathways. They may be present singly, or in any combination, within a particular bacterial species. These are summarized in Table 1.

**The problem of resistance**

The risk of acquiring infection with antibiotic resistant organisms is positively correlated with increasing age, illness severity and debility, prolonged ICU stay, prior antibiotic usage, and exposure to indwelling prosthetic devices—principally central venous catheters and tracheal tubes. Unsurprisingly, the most common infections acquired on the ICU are ventilator-associated pneumonia (Gram +ve and Gram –ve), and line-associated bacteraemia (principally Gram +ve).

Inappropriate antibiotic selection is strongly associated with increased mortality; therefore, infection with resistant organisms can be associated with poor outcome if initial antibiotic selection does not provide coverage. There is an increased mortality rate in patients with ventilator-associated pneumonia caused by multi-drug-resistant organisms.

Most ICU’s will have antimicrobial policies that guide the selection of antibiotics. These are based on risk factors for the patient (including previous therapy, underlying condition, and relevant microbiology) and local epidemiology of resistant organisms. Regular input from medical microbiologists or infectious disease physicians is essential.

**Common resistance problems**

**Methicillin-resistant *Staphylococcus aureus***

This organism has a high political profile, with trusts in England recently set targets for bacteraemia rates. Patients developing
methicillin-resistant *Staphylococcus aureus* (MRSA) infection commonly have more underlying diseases and a greater number of previous infections and antibiotic treatments.

Several authors have investigated whether MRSA infection has an excess mortality. Overall mortality rates in patients with MRSA infection are higher than in those with methicillin-sensitive infection; however, once corrections are made for co-morbidities, there is no significant excess mortality and patients tend to die with rather than of their MRSA infection.1

Despite this, it is clear that MRSA infection is associated with greater healthcare costs—be that from longer hospital stays, greater numbers of interventions and more expensive antibiotic therapies. Recent comprehensive guidance on the management of MRSA infection has been issued.6

**Extended-spectrum β-lactamase-producing organisms**

Extended-spectrum β-lactamase-producing organisms (ESBL) is a plasmid-mediated form of resistance in Gram-ve bacteria to the β-lactam antibiotics. Until relatively recently, the clinical problem was small, stable (at least in the UK), and largely restricted to *Klebsiella* isolates in high-risk hospital patients. Since 2004/5, a new, highly resistant ESBL (CTX-M) has emerged in *Escherichia coli* and *Enterobacter*, responsible for significant outbreaks of resistant, community-based infection, often of the urinary tract. Mortality in these patients has been high. ESBLs (a term for any infection with bacteria possessing ESBL) have been reported in almost every European country. The global prevalence is approximately 25%, with higher figures for Mediterranean countries and as little as 3% for the USA. ESBL-carrying bacteria can also have other resistance mechanisms (e.g. membrane protein deficiencies) and resistance to other classes of antibiotic (e.g. the aminoglycosides, and quinolones trimethoprim/sulfamethoxazole).

Carbapenems are currently the most active class against ESBL bacteria, because of their stability against the hydrolytic effects of the β-lactamase.

**Vancomycin-resistant Enterococci**

The enterococci, *Enterococcus faecalis* and *Enterococcus faecium*, are normal bowel commensals in humans and animals. They are generally of low virulence causing serious infection in debilitated, immunosuppressed patients, with little risk to healthy individuals. Common sites of infection are the urinary tract, peritoneal cavity, and surgical wounds. Rarely, they present as a bacteraemia or endocarditis.

Vancomycin-resistant enterococci (VRE) were unknown before 1986 (identified in France), but have since populated the world, comprising 47% of isolates in one recent study. A direct effect on mortality is debatable once confounding variables are considered. Recent studies correcting for these have concluded that Vancomycin resistance *per se* does not carry an excess mortality; these isolates are no more virulent, just more difficult to eliminate. However, infection is associated with longer ICU and total hospital stay.

**Other Gram-ve organisms**

Acinetobacter species (commonly ‘Baumannii’) are ubiquitous in the environment and, in general, of low virulence. Their ‘targets’ are similar to those already described with preponderance to nosocomial pneumonias.

They seem particularly skilled at acquiring multi-drug resistance and, worryingly, have been linked to infection outbreak in ‘healthy’ populations, suggesting the acquisition of virulence. Carbapenem resistance, while about 5% in the UK, is >50% in South America and the Middle East.

*Stenophomonas maltophilia*, a bacterium originally classified as a pseudomonas, is also found in many environments and has very low virulence. Immuno-compromised patients are at increasing risk with the predictable spectrum of infection. Treatment is difficult because of multiple drug resistance and strict hygiene/isolation is essential to prevent dissemination.

Of the many strains of *Pseudomonas*, *Pseudomonas aeruginosa* is most frequently associated with human infection. Again a ubiquitous Gram-ve rod with low natural virulence, infection is truly opportunistic with patients in ICU a common target. In many parts of the world the number one cause of nosocomial pneumonia, this organism has evolved multidrug resistance and may be very difficult to treat.

There are many other enterobactreacia responsible for nosocomial infections, all largely opportunistic and with varying degrees of multiple resistance.

Table 2 describes resistant organisms.

**Management strategies**

From this brief consideration of possible mechanisms, it is apparent that no single measure can be effective in the prevention of infection due to antibiotic resistant organisms or reduction of resistance. Knowledge of the mechanism of transmission of resistance enables targeted efforts to control outbreaks. For example, if resistance is being imported, greater isolation and screening measures should be employed. Alternatively if resistance is being disseminated from within the unit, better adherence to infection control measures should be enforced.

A wide range of non-pharmacological methods are employed to try and limit the spread of resistant infections. These are to be covered elsewhere, and will not be discussed further in this review.

**Selective decontamination of the digestive tract**

Selective decontamination of the digestive tract (SDD) is not commonly practiced within the UK health care environment despite evidence that the incidence of ventilator-associated pneumonia may be reduced. Meta-analysis have demonstrated a reduction in the odds ratio for lower airway infections to 0.35 (0.29–0.41) and a 6% overall mortality reduction to 24% without an increase in superinfections because of resistant bacteria.7
A recent comprehensive review\(^8\) proposed four key recommendations:

- SDD should be considered when it is anticipated that mechanical ventilation will be required for more than 48 h.
- SDD regimens should include topical and parenteral agents with activity against Gram-ve bacilli; the choice of treatment should depend on local pathogen antimicrobial susceptibility profiles.
- The use of SDD should not be withheld because of concern about the development of antibiotic resistance.
- SDD should be supported by good infection control and planned prospective susceptibility surveillance so that problems can be identified early and addressed.

### Antibiotic cycling

This is the planned withdrawal of commonly used antibiotics for a scheduled period (e.g. 6 months), to reduce selection pressure and the emergence of resistance. Different suites of antibiotics are then used which are themselves changed after 6 months. Raymond and colleagues\(^9\) prospectively studied the effect of a quarterly empiric antibiotic rotational schedule in a surgical and trauma ICU. They devised a simple rotating antibiotic class schedule for the empirical treatment of pneumonia and peritonitis or sepsis of unknown origin. Compliance was high, and they were able to demonstrate a statistically significant decline in the incidence of resistant infections. This included gram positive (\(S. aureus\), \(S. epidermidis\), and \(S. enterococcus\)) and gram negatives (\(Pseudomonas\) and \(Acinetobacter\)). A reduction in infectious (2.9 deaths per 100 admissions vs 9.6, \(P = 0.0001\)) and overall mortality (15.5% vs 38.1%, \(P = 0.0001\)) was seen. Rates of vancomycin resistance were unchanged, however, and there was no significant decrease in duration of hospital stay.

### Restrictive antibiotic strategies

External oversight of antibiotic prescribing has been advocated by some authors. They argue that ICU’s that are manned by relatively junior physicians that rely on a relatively small pool of antibiotics. Additionally, they are more likely to treat every bacterial isolate received on patients, when many such results may be evidence of colonization rather than true infection. Mechanisms proposed include the use of infection scoring for the diagnosis and treatment duration of ventilator-associated pneumonia, and the use of bronchoscopic lavage to isolate the causative organisms of pneumonia. If gram stain is negative or significant bacterial culture is not seen with samples obtained at BAL, antibiotics are stopped. This strategy led to a significant reduction in mortality (16.2% mortality vs 25.8% control, \(P = 0.022\)) in a study by Fagon and colleagues.\(^10\) An alternative strategy involves external supervision of antibiotic therapy by an Antibiotic Stewardship Team, consisting of medical microbiologists/infectious disease physicians and pharmacists.
De-escalation

Many studies have shown in severe infections, particularly nosocomial pneumonia, that inadequate initial antibiotic therapy is associated with increased mortality. As other risk factors for mortality may not be amenable to modification by the treating physician (these being length of inpatient stay and presence of co-morbidities), adequate initial antimicrobial treatment is paramount. Furthermore, research has shown that subsequently altering prescriptions to provide adequate cover does not significantly alter outcomes. Consequently, broad-spectrum agents are often used as initial therapy. The disadvantage of this is the increased risk of developing resistant infections when broad-spectrum use is widespread. Hoffken reviewed the literature regarding de-escalating strategies in the treatment of pneumonias in ICU, and demonstrated that targeting treatment and limiting duration may reduce cost without affecting outcome.

Microflora surveillance

Microflora surveillance has shown that the range and frequency of micro-organisms isolated varies between institutions and even within an ICU over time. The collection of regular microbiological data allows a picture of common pathogens and their antibiotic sensitivities to be collected, with clear therapeutic advantage.

The importance of correct dosing

Recent work has sought to characterize optimal dosing strategies through the use of pharmacokinetic data. Put simply it means that adequate doses are important, and underdosing should be avoided.

Clostridium difficile

The choice of antibiotic is further complicated by increasing concerns about C. difficile.

Recent large-scale outbreaks, particularly among elderly medical inpatients, have raised awareness and an increase in incidence and severity of disease has been noted. Possible explanations for this are antibiotic misuse (particularly cephalosporin and quinolones), the development and dissemination of strains with increased virulence, and failures in basic infection control strategies.

Management includes immediate isolation and confirmation of cases with stool sample toxin assays (24–48 h). Treatment is preferably with oral antibiotics (metronidazole or vancomycin). If the oral route is unavailable, i.v. administration is a viable although less efficacious alternative.

Practical measures

As discussed, the development of antimicrobial resistance in an intensive care setting has multiple causes. Strategies to counter these include:

- New admissions to ICU should be screened for target organisms and wherever possible isolated to prevent the introduction of resistant strains.
- Strict infection control measures including isolation, hand washing, and minimizing the number of nursing and medical staff involved in each patients’ care.
- Regular surveillance of the local microflora and resistance patterns occurring within the ICU should be performed, leading to regular review of empirical antibiotic guidelines.
- Before administration of antibiotics, sufficient cultures should be sent to facilitate microbiological identification. Bronchoscopy should be considered if pneumonia is suspected to enable better sputum samples to be sent and improve microbiological isolation.
- Prescriptions should be reviewed after 2–3 days. Antibiotic therapy may then be altered according to sensitivity information, or stopped altogether if no organisms have been isolated and the clinical picture allows it.
- Oversight of antibiotic prescriptions by ICU pharmacists and Microbiologists may prevent inadequate dosing regimens and reduce inappropriate prescriptions.

References

7. van Saene HKF, Peters AJ, Ramsay G et al. All great truths are iconoclastic: selective decontamination of the digestive tract moves from heresy to level one truth. Int Care Med 2003; 29: 677–90

Please see multiple choice questions 10–14