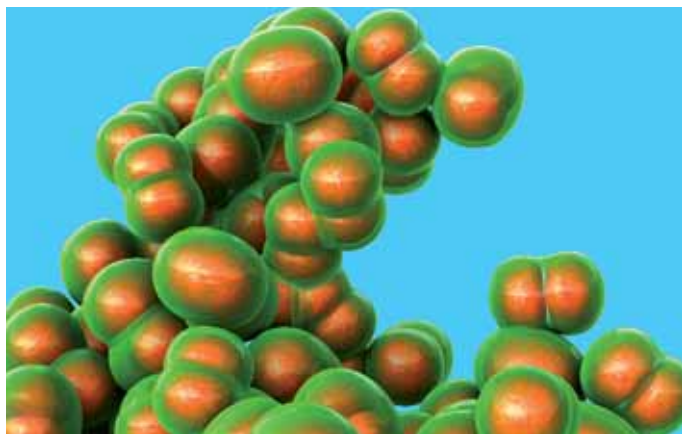


Healthcare-associated infection

— hospital-acquired infection

By Conor Jamieson, PhD, MRPharmS

Healthcare-associated infections represent a massive challenge currently facing the NHS. Pharmacists must play their part in the management of infected patients and be aware of strategies that prevent one infection becoming an outbreak



ROGER HARRIS/SPL

Meticillin-resistant *Staphylococcus aureus* infections are one of the biggest problems for healthcare providers worldwide

Recent outbreaks of uncontrolled healthcare-associated infection (HCAI) have demonstrated the devastating impact that such infections can have on the health services operationally, politically and in terms of patient morbidity and mortality.

HCAIs are defined as infections acquired while in hospital or because of healthcare interventions. This article focuses on hospital-acquired infections — those that develop as a result of exposure to organisms that thrive in a hospital environment. However, if the infecting organism is introduced to the body by an invasive healthcare intervention, it is considered an intervention-related infection. This is discussed separately (p13).

A hospital-acquired infection is one that develops at least 48 hours after a patient is admitted to hospital, or up to 48 hours after discharge. Outside this period, infections are considered to be community-acquired.

Political drive Controlling HCAIs is a key focus for the Department of Health, which in 2004, announced a target to halve the national incidence of MRSA (meticillin-resistant *Staphylococcus aureus*) infections by 2008 (based on figures for 2003). Guidance on reducing HCAIs has been published by the DoH and trusts are now required to produce frequent reports on HCAI incidence rates. Another HCAI that will be

included in these reports is *Clostridium difficile*-associated diarrhoea, for which the national incidence is continuing to increase.

The inclusion of the Hygiene Code in the Health Act 2006 placed a legal requirement on NHS managers to prevent and control HCAIs, and provided criteria to ensure a clean environment for patients, in which the risk of HCAIs is as low as possible. However, working to prevent and control HCAIs is the responsibility of all members of the healthcare team.

— MRSA

Beta-lactam antibiotics (eg, penicillins, cephalosporins) kill bacteria by inhibiting the action of penicillin-binding proteins, essential for maintaining a viable cell wall. MRSA has evolved to develop a penicillin-binding protein that continues to function in the presence of beta-lactam antibiotics. *S aureus* is believed to have acquired the gene for this mutation from a related staphylococcal species.¹

MRSA was first recognised in the 1960s² but is now one of the biggest problems in healthcare worldwide. The ability of MRSA to acquire resistance to other antibacterial agents through genetic transfer resulted in limited treatment options during the 1980s and 1990s, but the arsenal of anti-MRSA agents has since expanded. Recent data from the Health Protection Agency demonstrated that the incidence of MRSA bacteraemia in the UK during 2006–7 was 12 per cent lower than in 2001–2.

Source of infection Staphylococci are part of the skin's natural flora. Detecting MRSA on the external surfaces of the body (eg, nose, groin and axillae) indicates colonisation, not necessarily infection. Although MRSA colonisation is not life-threatening, it is a significant risk factor for developing the infection or for infecting other patients or staff.³

Traditionally, MRSA has been considered a hospital-acquired infection, developing during or after contact with hospitals or care homes. In practice, 65 per cent of MRSA bacteraemias are acquired during hospital admission,⁴ often due to failures in infection control. However, other risk factors include prolonged hospital stay, the use of invasive medical devices (eg, venous catheters) and treatment with certain antibiotics,⁵ in particular:

- Quinolones
- Cephalosporins
- Macrolides

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Panel 1: The advantages and disadvantages of antibacterials with activity against meticillin-resistant *Staphylococcus aureus*

Antibacterial	Advantages	Disadvantages
Vancomycin	Bactericidal, known side effect profile, cheap	Requires therapeutic drug monitoring (TDM) and dosage adjustment in renal failure, intravenous delivery only
Teicoplanin	Bactericidal, once-daily administration allows use in outpatient setting	Requires TDM to ensure adequate serum levels, IV and intramuscular delivery only
Linezolid	Oral delivery, possibly more effective than vancomycin for treating pneumonia	Risk of bone marrow toxicity, bacteriostatic, some resistance has developed
Tigecycline	Broad spectrum of activity allows for monotherapy in mixed infection	No activity against urinary tract infections, IV delivery only, bacteriostatic
Daptomycin	Bactericidal, once-daily administration	IV delivery only, no activity against pneumonia
Fusidic acid	Good concentrations in bone	Resistance has developed with monotherapy, liver toxicity, thrombophlebitis

Community MRSA A distinct strain of community-acquired MRSA is now recognised among patients that have not had prior contact with healthcare institutions.⁶ This strain of MRSA is usually susceptible to a wider range of antibiotics than its hospital-acquired counterpart. However, it is more likely than hospital-acquired MRSA to carry a virulence factor known as Panton-Valentin leucocidin. This toxin damages white blood cells and infection can cause severe skin disease, septic arthritis and necrotising pneumonia.⁷

Treatment Glycopeptides have been the main treatment of MRSA infection for 40 years, but there is now an increasing number of agents available with activity against MRSA, as shown in Panel 1. In addition, several agents are undergoing clinical trials. These include:

- Ceftobiprole — a cephalosporin with activity against MRSA
- Telavancin — a glycopeptide that can be given once daily
- Dalbavancin — a glycopeptide that can be given once weekly

Several oral agents have activity against MRSA, such as doxycycline, trimethoprim, fusidic acid and rifampicin. Combinations of these drugs are commonly used to treat MRSA skin infections.

Patients identified as being colonised with MRSA should be isolated whenever

possible and prescribed a decolonisation regimen. For example:

- Mupirocin nasal ointment — to eliminate the organism from the nose
- Chlorhexidine or triclosan topical wash — to eliminate the organism from the skin

Result of infection MRSA infection can cause a spectrum of disease, ranging from simple urinary tract infections and cellulitis to life-threatening bacteraemia and endocarditis.

MRSA bacteraemias should be carefully investigated to determine the source of infection, because the formation of septic emboli can cause a deep-seated infection such as an abscess, discitis or endocarditis. The British Society for Antimicrobial Chemotherapy (BSAC) has produced guidelines for treating MRSA infection, from which the main recommendations are listed in Panel 2.

The role of pharmacists Pharmacists have a key role in monitoring patients who have been colonised or infected with MRSA. For example, ensuring decolonisation regimens are prescribed correctly, advising on therapeutic drug monitoring for glycopeptides and monitoring side effects.

— ESBL

Overuse of antibiotics in modern healthcare has led to certain bacteria developing ESBLs (extended-spectrum beta-lactamases) — enzymes that destroy beta-lactam antibacterials.

Cephalosporins have traditionally been resistant to hydrolysis by beta-lactamases because they contain bulky side chains that prevent interaction with the enzyme's active site. However, ESBLs have become capable of hydrolysing cephalosporins due to point mutations that have enlarged the size of the active site.

ESBLs represent an evolutionary response that is exclusive to Gram-negative bacteria. Although originally produced by *Klebsiella* spp, the enzyme is now increasingly common among *Enterobacteriaceae* spp. There are now over 200 types of ESBL,⁸ and one common UK strain (CTX-M-15) is capable of destroying cefotaxime and ceftriaxone.⁹

Patients who have taken a recent course of antibiotics, either before or during a hospital

Panel 2: Summary of the British Society for Antimicrobial Chemotherapy recommendations for treating MRSA infections

Site of infection	Recommended antibacterials
Urinary tract	Tetracyclines, trimethoprim, nitrofurantion
Skin and soft tissue	Tetracyclines if low risk of bacteraemia Vancomycin or linezolid if high risk of bacteraemia
Respiratory (pneumonia)	Vancomycin or linezolid
Cardiac and sepsis	Vancomycin or linezolid
Prosthetic joint	Intravenous: vancomycin plus rifampicin or fusidic acid Oral: rifampicin plus fusidic acid or fluoroquinolone or trimethoprim If erythromycin-sensitive: clindamycin
All recommendations assume that sensitivity to the recommended agent is confirmed	

stay, should be considered at risk of infection with ESBL. Such infections can also be resistant to quinolones and aminoglycosides.

Treatment Successful treatment often requires a determination of the organism's antibacterial sensitivities. Beta-lactamase inhibitors such as clavulanic acid and tazobactam can inhibit ESBLs, however some strains have become capable of producing an inhibitor-resistant beta-lactamase as well.⁹ Therefore, penicillin and beta-lactamase inhibitor combinations (eg, Tazocin) are not always successful.

Carbapenems, such as meropenem, are often the treatment of choice for severe infections, while tigecycline and temocillin are new options for intravenous therapy.

Early administration of an active agent reduces mortality in bacteraemia.¹⁰ A review of ESBL-producing *Klebsiella pneumoniae* bacteraemias found that empiric treatment of the infection with non-active antibiotics (which in the review were continued for five days) caused a significant increase in mortality. Non-severe conditions (eg, uncomplicated urinary tract infections) can often be treated with oral mecillinam or nitrofurantoin — providing the infecting organism is not resistant.

As with MRSA, isolation and appropriate barrier precautions will be required for patients who are colonised or infected with ESBL-producing bacteria.

— Clostridium difficile

Part of the normal gut flora, *Clostridium difficile* is a spore-bearing, Gram-positive bacterium. A disturbance to the composition of gut flora can lead to overgrowth of *C difficile* and increased production of its two toxins, which damage the gut wall. This can cause mild diarrhoea or the potentially fatal complications of pseudomembranous colitis and toxic megacolon. Bacterial spores can contaminate hospital wards and spread the infection rapidly between patients.

A growing problem Despite increased awareness of this problem, the incidence of *C difficile*-associated diarrhoea (CDAD)

Suggestions for future special features

If you would like to suggest a topic for a future special feature in *Hospital Pharmacist*, or if you are a specialist clinical pharmacist interested in writing about your area of practice, please contact Hannah Pike (e-mail hannah.pike@pharmj.org.uk, telephone 020 7572 2425) or Gareth Malson (e-mail gareth.malson@pharmj.org.uk, telephone 020 7572 2419).

Panel 3: Summary of the British Society for Antimicrobial Chemotherapy guidance for treating hospital-acquired pneumonia

Classification or cause of infection	Recommended antibacterials
First line early-onset with no risk factors for acquiring pneumonia	Co-amoxiclav or cefuroxime
Second line early-onset or first line with one or more risk factors	Cefotaxime or ceftriaxone, fluoroquinolone, Tazocin (piperacillin and tazobactam)
<i>Pseudomonas aeruginosa</i> — suspected or proven	Ceftazidime, ciprofloxacin, meropenem or Tazocin
Meticillin-resistant <i>Staphylococcus aureus</i> — suspected or proven	Glycopeptide (eg, vancomycin, teicoplanin) or linezolid
Late-onset	No specific suggestion, empirical antibacterials should be chosen according to local pathogens

continues to rise.⁴ During 2006, 7 per cent more cases were reported in the UK compared with 2005. However, this was an improvement on the 16 per cent increase between 2004 and 2005.

The rise in infection rates may have been caused by the emergence of a hyper-virulent strain known as 027, which overproduces its toxins and causes a more severe and relapsing illness. This strain is responsible for many outbreaks across the world, most notably in Quebec, Canada, between 2002 and 2005. Infected patients carried a 16.7 per cent greater risk of mortality during the year after infection, compared with case-matched controls.¹¹

Such outbreaks can have a major financial impact on the hospital by increasing the duration of hospital admissions. In 2002, the cost of treating one case of CDAD was estimated to be £4,200.¹²

Patients at risk CDAD is most common among elderly patients — 84 per cent of cases affect patients aged 65 years or over.⁴ However, other risk factors for infection include:

- Treatment with antibiotics
- Proximity to infected patients
- Use of proton pump inhibitors
- Receiving chemotherapy
- Undergoing surgery

Antibacterial use Much blame has been placed on fluoroquinolones (eg, ciprofloxacin, levofloxacin) and third-generation cephalosporins for causing increased infection rates. The common association between these antibacterials and CDAD may be explained by the fact that they are commonly used in hospitals. However, guidance has been published by the DoH that suggests the use of these drugs should be limited.

Treatment For many years, metronidazole has been preferred to oral vancomycin for treating CDAD, due to its comparable efficacy, lower cost and the potential emergence of vancomycin-resistant enterococci. A recent trial suggested that metronidazole is inferior to vancomycin for severe disease.¹³ However the trial design has been criticised.

Therapies under development for treating infection include:

- Rifamixin — a non-absorbed antibiotic
- Tolevamer — a drug that binds *C difficile* toxins to prevent diarrhoea

Adjunct treatment for infection include immunoglobulins, toxin-binding agents (eg, colestyramine) and probiotic supplements. However results are confounded by small-sized or poorly designed trials and as yet, no consensus has been reached on the efficacy of these treatments.

— Pneumonia

If a patient develops pneumonia in hospital at least 48 hours after admission, it is defined as hospital-acquired pneumonia (HAP). Hospital patients may also suffer from ventilator-associated pneumonia.

HAP can range from a mild infection to severe disease that requires admission to intensive care. It affects about 2 per cent of inpatients and increases the hospital stay by up to nine days.¹⁴ HAP can be divided into early-onset and late-onset, depending on whether it develops within or after five days of admission.

Infecting organisms Early-onset HAP is usually caused by a known range of organisms, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and the *Enterobacteriaceae* spp.

Late-onset HAP is caused by a wider range of organisms, including MRSA, *Pseudomonas aeruginosa*, and other Gram-negative organisms.

Diagnosing HAP is difficult and usually relies on the patient displaying clinical evidence of sepsis or radiographic changes in the chest. Microbiological sampling from sputum or broncho alveolar lavage is recommended for identifying causative organisms.

Treatment BSAC has produced guidance on antibacterial choice for treating HAP, and this is summarised in Panel 3 (p10).

Ventilator-associated pneumonia When a patient is mechanically ventilated, micro-organisms can bypass some of the respiratory tract's infection defences. Since the patient lies in a supine position for long periods and is often comatose, VAP can develop, which is fatal in 15–55 per cent of cases.¹⁵

The diagnosis of VAP is similar to HAP, and is based as much on clinical judgement as on the interpretation of radiographic features. Microbiological sampling should be performed to ensure that the condition is treated with appropriate antibacterials. The species of the causative organism (eg, *P aeruginosa*, MRSA) will depend on previous antibacterial therapy and the duration of intubation.

— Norovirus

Noroviruses are a group of round-structured viruses that can cause outbreaks of gastroenteritis. They are also known as “winter vomiting viruses” and “Norwalk-like viruses”.

Infection with norovirus causes symptoms within 12–48 hours, which typically consist of sudden nausea followed by projectile vomiting and watery diarrhoea.

The infection is usually self-limiting, and most patients recover within a few days. However, in severe cases or vulnerable patients (eg, young children or the elderly), severe dehydration can occur and hospital treatment may be necessary.

Cause of infection Norovirus is easily transmitted by several vectors:

- Aerosol formation during vomiting
- Contamination of surfaces or objects with infected vomit or diarrhoea
- Consumption of contaminated food or water

The virus can survive outside the human body for several days, and can cause sporadic outbreaks by circulating through close communities.

The close proximity of patients within a hospital ward promotes the spread of infection between patients and staff. This

can result in ward closures, cancellation of procedures and operations (due to staff illness) and an effect on hospital admission targets. The management of other HCAs can also become problematic if isolation facilities are filled. Despite this, the significance of infection is not widely recognised by the public or among hospital staff.

Outbreak management Successful management of a hospital outbreak of norovirus requires:

- Recognising the outbreak early
- Isolating symptomatic patients
- Employing effective barrier precautions for staff (eg, gloves and aprons)
- Scrupulous hand washing with soap and water
- Preventing the transfer of symptomatic patients to unaffected areas of the hospital

In practice, this usually requires closing the ward to new admissions and postponing discharges until 48 hours after the symptoms of the last affected patient have resolved.

Role of pharmacists Pharmacists can help manage outbreaks by remaining vigilant to incidences of vomiting and diarrhoea and adhering to guidance on hand hygiene and barrier precautions.

Close liaison with infection-control staff is vital to ensure the pharmacy department remains informed about the situation and reduces the risk of staff shortages due to illness that could impact on other areas of the hospital.

— Conclusion

Healthcare-associated infections present a considerable challenge for health services. They cause significant concern for patients and attract substantial media and political attention. Good infection control practice is the responsibility of all healthcare staff and is only achieved through awareness and teamwork.

Pharmacy staff should remain aware of local infection control policies and ensure they are followed. Pharmacists will contribute to the management of infected patients and should have a good working knowledge of local antibiotic guidelines.

Good communication between the pharmacy, infection control and microbiology departments will facilitate appropriate patient management and help to reduce the incidence of HCAs.

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