Effective strategies for prevention and control of Gram-negative infections


Summary
Infections caused by Gram-negative bacteria such as Pseudomonas, Klebsiella, Proteus and Acinetobacter have been a major problem in healthcare settings for many years. Overlooked in government targets and unknown to patients, these infections present considerable challenges for effective infection prevention and control. Key strategies for prevention and control focus on contact precautions, the management of invasive devices and maintaining a clean, dry environment to prevent the build-up of environmental reservoirs and cross-infection.

Author
Dinah Gould is professor in applied health, St Bartholomew School of Nursing and Midwifery, City University, London. Email: D.Gould@city.ac.uk

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Gould-positive and Gram-negative bacteria

Although penicillin was discovered in 1928 it was not widely introduced into clinical practice in the UK until the 1940s (Selwyn 1991). The original penicillins, such as benzylpenicillin, were derived from naturally occurring sources and were active only against Gram-positive bacteria (Box 1), which were the major nosocomial pathogens at the time. Once these infections had been controlled, an environment was created that favoured the growth and multiplication of Gram-negative species, and these began to cause problems not previously anticipated (Harris et al 1969).

BOX 1
Gram-positive and Gram-negative bacteria

The Gram stain reaction is an important laboratory test used to identify bacteria. It is clinically important because it distinguishes structural differences between those bacteria able to take up the stain (Gram-positive species, such as staphylococci and streptococci) and those that do not (Gram-negative species). As well as helping to identify bacteria, the Gram stain provides an indication of their behaviour. For example, Gram-positive bacteria are generally better able to withstand dry conditions than Gram-negative bacteria.
Initially Gram-negative bacilli were considered to have low levels of pathogenicity, but a series of carefully documented epidemiological studies described by Lowbury et al (1970) suggested that spread could occur rapidly in the warm, damp clinical environment, which is ideally suited to the rapid growth and reproduction of Gram-negative bacilli.

The results of these investigations indicated that spread was occurring by direct contact via the hands of staff and other objects in the clinical environment (Box 2). There was evidence that hands and items in close patient contact became rapidly and often heavily contaminated leading to cross-infection (Lowbury et al 1970). Nurses’ hands frequently became contaminated with bacteria of the same strains as those colonising patients’ skin and causing infection in wounds, urinary catheters and ventilator tubing (Casewell and Phillips 1977). Cross-infection was prevented when strict regimens of hand hygiene were introduced (Casewell and Phillips 1978).

With the passage of time numerous different types of Gram-negative bacteria emerged as potential pathogens and outbreaks were reported from a wide range of different clinical settings, from acute care to long-stay wards (Gould and Chamberlain 1994). Substantial numbers of Gram-negative infections continue to be reported, disrupting the delivery of care, contributing to the distress of patients and families and increasing costs to the health services in the UK and other countries (Bou et al 2009). Therefore an understanding of the risks and consequences of Gram-negative infection and how to prevent them remain paramount to all nurses.

**Gram-negative bacteria**

The main clinically significant Gram-negative bacteria causing HCAI are: *Pseudomonas*, *Klebsiella*, *Escherichia coli*, *Proteus*, *Acinetobacter* and *Serratia*. They are found widely in the environment in soil, on plant material, and often inhabit the human gastrointestinal tract harmlessly. The ability of Gram-negative bacilli to withstand the action of many of the commonly used antibiotics and disinfectants, and the symptoms they cause is explained by the structure of their cell walls (Figure 1).

The cell wall of Gram-negative bacteria consists of lipids, polysaccharides and amino acids, surrounded by an outer membrane composed of protein, phospholipids and lipopolysaccharides. The presence of the outer membrane enables Gram-negative bacteria to resist penetration by many harmful chemicals, including disinfectants that are used widely in hospitals. However, because their cell walls have a much thinner peptidoglycan layer than Gram-positive bacteria they are more susceptible to desiccation, with the exception of *Acinetobacter spp*. Therefore the growth and reproduction of Gram-negative bacteria can be controlled by maintaining a dry environment.

Maintaining a clean environment is also central to successful control because their growth requirements are undemanding: Gram-negative bacilli thrive readily in the presence of only a few inorganic ions and moisture (Pettit and Lowbury 1968). Environmental contamination occurs readily leading to reservoirs of infection when favourable conditions promote their growth and reproduction (Gould and Chamberlain 1994).

Reservoirs of Gram-negative bacteria can form on the skin of staff or patients, leading to cross-infection. The contribution of environmental reservoirs to HCAI depends on their situation. A large reservoir of bacteria down a drain is unlikely to be of clinical significance because there is little risk of them being transferred to staff or patients (Levin et al 1984). Conversely, if the reservoir involves objects or sites that will come into contact with staff or patients, the risks are considerable. Heavily contaminated flannels and

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**BOX 2**

Items frequently contaminated with Gram-negative bacteria

- Baths.
- Bedpans and commodes.
- Catheter drainage bags.
- Flannels.
- Hoists.
- Mattresses.
- Respiratory equipment, for example humidifiers.
- Urinals.
- Washbowls.

**FIGURE 1**

Cell wall of a typical Gram-negative bacterium

- Peptidoglycan layer
- Membrane protein
- Cytoplasmic membrane
- Sugar molecules
- Phospholipid
- Lipoprotein
- Outer membrane

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towels have resulted in cross-infection to patients and nurses (Sanderson and Weissler 1990).

Once the bacteria have been transferred to a susceptible patient they can ascend to the bladder especially if an indwelling urinary catheter is in situ, colonise the gastrointestinal tract, appear in the faeces and can be transferred from the oropharynx to the lower respiratory passages, causing pneumonia. Other serious infections caused by Gram-negative bacteria include septicemia and peritonitis.

Gram-negative bacilli are usually only weakly pathogenic, causing infection in people who are already sick. They are unlikely to cause infection in healthy people, although they can be carried on the skin for long periods, particularly if it is damaged (Sanderson and Weissler 1990). They often colonise sites where the body’s normal defence mechanisms are breached, for example as a result of urinary catheters, intravenous cannulae, and endotracheal tubes. If the numbers present are able to increase, the host defenses are compromised and infection supervenes.

The risks and consequences of Gram-negative infection are higher for patients who have a large number of indwelling devices that bypass the body’s usual barriers to invading pathogens. Patients in intensive care units, neonatal intensive care units and burns units are at particular risk. When outbreaks of Gram-negative infection occur they are controlled by monitoring and improving general standards of hygiene and cleanliness (Gould and Chamberlain 1994), including hand hygiene (Casewell and Phillips 1978).

The symptoms of Gram-negative sepsis are caused by an endotoxin called lipid A. Endotoxin A is present in the outer membrane surrounding the cell wall and is toxic. It is released when the bacteria die and causes severe illness (toxemia) if it enters the circulation. The patient experiences malaise and fever when the bacteria enter the bloodstream. Multiplication of live bacteria in the bloodstream causes septicemia.

**Antibiotics and Gram-negative infection**

Over the years a range of synthetically derived penicillins has been developed including: benzylpenicillin, ampicillin, amoxicillin, flucloxacillin, ticarcillin, piperacillin, and piperacillin with tazobactam. Unlike the early, naturally derived penicillins, these broad spectrum antibiotics are effective against Gram-positive and Gram-negative bacteria. Nevertheless, both the original and synthetic penicillins operate in the same way. They bind to a protein called penicillin-binding protein important in the production of peptidoglycan, thus preventing formation of the bacterial cell wall. Its integrity is disrupted and the cell is killed.

Penicillin and its derivatives are often referred to as beta-lactam antibiotics after the beta-lactam ring that forms an important part of their molecular structure. Cephalosporins have a similar chemical structure to penicillins, including a beta-lactam ring. Second generation beta-lactamase-resistant cephalosporins developed in the 1970s, such as cefuroxime, have a broad spectrum.

**Emerging problems**

Gram-negative bacteria have caused troublesome infections since the 1950s, and now new problems are emerging. Changing approaches to health care and the way that the bacteria are adapting to exposure to antibiotics in the clinical environment are presenting new infection prevention and control challenges.

**Changing approaches to health care**

Advances in technology have provided novel approaches to the delivery of health care. For example, innovation in mobile communication technology has improved the speed and quality of routine communication, but has introduced new infection risks. There is an increasing tendency for clinical staff to bring mobile communication devices (MCDs) into the clinical setting and to use them in patient care areas, including high-risk areas such as intensive care and operating theatres.

A review of the literature has demonstrated that MCDs can become heavily contaminated with a range of pathogenic bacteria including Gram-negative bacilli, and that the bacteria are of the same type as those on the owner’s hands (Brady et al 2009). Although there is no evidence that patients have developed infection from MCDs, it is clear that the potential exists, especially as the best method of cleaning MCDs remains to be established and staff appear highly resistant to suggestions that MCDs should not be used in clinical areas (Brady et al 2009).

Other non-clinical equipment such as computer keyboards also become heavily contaminated with bacteria, including Gram-negative bacilli and may have the potential to operate as reservoirs (Bures et al 2000). As the use of MCDs and computers as adjuncts to patient care increase, it is inevitable that new and increasing risks of cross-infection will continue to emerge.

A second problem is ‘upskilling’ in which patient care activities traditionally undertaken by qualified nurses have been assumed by staff who lack the training necessary to identify and reduce infection risks (Gould 2005). Supervision of these staff is essential to ensure compliance with infection prevention and control protocols.
Selective pressures and bacterial adaptation

The widespread and sometimes unjustified use of broad spectrum antibiotics, such as the modern synthetic penicillins, has encouraged the survival and multiplication of resistant bacterial strains that are able to withstand their action (Selwyn 1991). Resistance occurs because the bacteria are able to produce an enzyme that destroys the β-lactam ring.

At one time this ability appeared to be restricted to Gram-positive bacteria, notably staphylococci, but now there are increasing reports that many types of Gram-negative bacteria, including Klebsiella spp and E.coli have acquired resistance to penicillins and are becoming difficult to treat not only in hospital (Cordery et al 2008), but also in residential homes for older people (Moor et al 2008). These bacteria are described as extended-spectrum β-lactamases (ESBLs). Risk factors for infection caused by ESBLs include: older age, recent antibiotic treatment, presence of an indwelling device such as a urinary catheter and having a co-morbid, chronic condition such as cardiovascular or neurological disease (Cordery et al 2008, Moor et al 2008). Resistance to any antibiotic can develop quickly in populations of Gram-negative bacteria because they multiply rapidly. Under ideal conditions a bacterium will divide into two new ones every 30 minutes.

Prevention and control

The successful control of Gram-negative infection depends on the meticulous application of traditional infection prevention and control measures including:

- Hand hygiene.
- Use of personal protective clothing.
- Isolating patients with antibiotic-resistant infections.
- High standards of environmental cleaning.
- Care of invasive devices.
- Supervision of junior and non-clinical staff.
- Education.
- Good practice in antibiotic prescribing.

The emergence of ESBLs reinforces the need for non-antibiotic approaches to infection prevention and control.

Hand hygiene, personal protective clothing and patient isolation Standard precautions should be taken to prevent the transmission of any infection spread by direct contact for all patients (for example, touching the skin and handling wounds), including Gram-negative bacteria. For patients with known infections disposable gloves and aprons should be worn whenever contact with an infected patient or the near-patient environment is anticipated; they must be discarded before contact with another patient. It is always necessary to wash hands and change gloves between ‘dirty’ and ‘clean’ procedures (Gould 2009). Patients who are colonised or infected with antibiotic-resistant strains may require isolation.

Maintaining a clean, dry environment Excellent standards of hand hygiene are confounded by high levels of contamination in the surrounding environment. Patient care items and equipment in the near-patient environment should be stored clean and dry to prevent cross-infection and the development of reservoirs (Gould and Chamberlain 1994). Flannels, towels and bedclothes should be changed frequently. Items, such as washbowls, should be reserved for individual use and stored upside down to allow any residual moisture remaining after use to drain away. Bedpans and urinals should be dealt with promptly. Local NHS trust policies should contain detailed information about cleaning patient care items. Bedpan washers and macerators should be serviced regularly and maintained in good working order. Suaces and bathrooms offer opportunities for the development of reservoirs of infection and should be cleaned frequently and thoroughly.

Care of indwelling devices Modern indwelling devices are designed to exclude invading pathogens, but at some stage it is necessary to gain access to the closed system, for example to empty a urinary catheter bag or to inject into an intravenous catheter. These activities should be undertaken using a strict aseptic technique. Colonisation and infection by Gram-negative bacteria are encouraged if devices remain in place for long periods. The need for the continuing presence of the device should be monitored continuously. Heavy colonisation or infection is a sign that the device should be removed.

Supervising junior and non-clinical staff Today, healthcare assistants are responsible for providing a major part of direct patient care, including help with personal hygiene, which offers major opportunities for environmental contamination and cross-infection (Sanderson and Weissler 1990). Although these activities might be devolved to healthcare assistants, the responsibility for providing a safe patient environment rests with the qualified nurse, who should assess and monitor the quality of care provided. Maintaining a clean, dry environment hostile to the development and perpetuation of reservoirs of Gram-negative bacilli forms an important part of the work of domestic staff. Monitoring their work is one of the key responsibilities of matrons, who are expected to liaise with ward staff and infection control teams to ensure that appropriate standards are met in England and Wales (Department of Health 2004).


art & science infection control focus

Education Traditionally, infection control nurses have provided clinical updating for staff in NHS trusts, but with the increased emphasis on infection prevention and pressure on their time, it might be necessary to commission other organisations to provide training and education. Input may be from a university or a company that provides infection prevention and control training. Quality control of the teaching is essential. Infection prevention and control experts and managers should ensure that the content and level of any teaching they commission are appropriate and that the topics covered reflect local NHS trust priorities, including the ever-present risks of Gram-negative infection, which might be overlooked in the continual struggle to meet government targets for MRSA and *C. difficile*.

Antibiotic prescribing In the case of acutely ill patients it is often necessary to administer a broad spectrum antibiotic until the bacteria responsible for infection have been identified and their sensitivity to different antibiotics has been determined. Once the causative organism has been identified, the narrowest spectrum effective antibiotic should be prescribed.

Policies have been developed to reduce the emergence of antibiotic-resistant bacterial strains. A typical policy in an NHS trust will include a selection of each of the main groups of antibiotic from which prescriptions are encouraged, and reserved exclusively that cannot be prescribed without liaison with the infection control team. The reserved antibiotics are not kept as ward stock. Excluding reserved antibiotics from routine clinical use reduces their exposure to bacteria and denies the bacteria opportunities to develop resistance.

Conclusion

Gram-negative infection has been a major problem in healthcare settings for many years and, despite increasing awareness of the importance of infection prevention and control, continues to present a significant challenge.

The cornerstones of effective preventive include unglamorous activities: meticulous application of contact precautions, management of invasive devices and monitoring the activities of staff to prevent the build-up of environmental reservoirs of bacteria and opportunities for cross-infection. Modern approaches to patient care, such as the increasing recognition of electronic and hand-held devices, increase the risks of cross-infection. The emergence of ESBLs represents a new and important challenge to patient safety.

References


