Infection prevention and control practitioners routinely address issues related to tuberculosis and multi-drug resistant organisms. Tuberculosis control involves engineering controls, administrative controls, and personal protective equipment. Many microorganisms have developed resistance to antimicrobials, making them less effective. Control measures vary by microbe. Infection prevention and control management of these various pathogens differs depending on the institutional setting and the resources available.
IFIC Basic Concepts of Infection Control

Introduction

Every-day problem microorganisms for infection prevention and control (IPC) practitioners include *Mycobacterium tuberculosis* and antibiotic-resistant microorganisms, namely methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Clostridium difficile*, and multi-drug resistant Gram-negative bacilli. Section A focuses on TB and Section B on antibiotic-resistant microorganisms.

**SECTION A: Tuberculosis**

Tuberculosis (TB) affects one third of the world’s population; in 2008 there were 9.4 million new cases and 1.8 million deaths, mostly in developing countries. It is the leading cause of death in individuals with human immunodeficiency virus (HIV). TB is caused by *Mycobacterium tuberculosis*.

**Pathogenesis and transmission**

Tuberculosis is spread by droplet nuclei travelling through the air when someone with active disease coughs, talks, sneezes, or spits. The bacteria are inhaled into the lungs and multiply in the alveoli; only a small number are needed to cause infection. Once in the body *M. tuberculosis* can travel to any location.

People infected with TB bacilli do not necessarily develop disease; the bacilli may be contained by the body’s host defences but remain alive-so-called latent TB. Approximately 10% of people with latent TB develop active TB when the bacteria subsequently grow and cause symptoms. The lungs are the most commonly infected organ. An untreated person with active pulmonary TB can infect 10-15 people a year. Other common sites of infection include the pleura, central nervous system, lymphatic system, genitourinary system, bones, and joints. TB outside the lungs is referred to as extrapulmonary TB and is not contagious.

Symptoms of pulmonary TB include a cough that brings up thick, cloudy, and, sometimes, bloody sputum, tiredness, appetite loss/unexplained weight loss, night sweats, fever/chills, and shortness of breath. In people with extrapulmonary TB, signs and symptoms vary with the site of infection.
Risk factors for TB include 1) illnesses that weaken the immune system, such as cancer and HIV; 2) close contact with someone with active TB; 3) caring for a patient with active TB; 4) living or working in crowded places like prisons, nursing homes, and homeless shelters where there are other people with active TB; 5) poor access to health care; 6) alcohol or drug abuse; 7) travel to places where TB is endemic; 8) being born in country where TB is endemic, and 9) some treatment medications for rheumatoid arthritis. Age too is important, the very young and the very old have naturally weaker immune systems.

**Diagnosis**

The tuberculin skin test (TST) can be used to determine infection with TB. It can take up to three months for a newly exposed individual to develop a positive TST. TB blood tests (also called interferon-gamma release assays or IGRAs) may be used to measure how the immune system reacts to the bacteria that cause TB. These tests cannot determine if a person has latent TB infection or active TB disease.

Bacille Calmette-Guérin (BCG) is a vaccine for TB. BCG vaccination may cause a positive reaction to the TST, which may complicate decisions about prescribing treatment. TB blood tests, unlike the TST, are not affected by prior BCG vaccination and are not expected to give a false-positive result in persons who have received prior BCG vaccination.

The management of patients with a positive test should occur in two steps: confirmation of a positive TST then referral for medical evaluation. This includes checking their medical history for potential exposures, demographic risk factors, and medical conditions that increase the risk of TB. Physical examination can be helpful, and a chest radiograph, although suggestive, is not confirmatory.

The standard method of diagnosis is microscopy of stained smears (e.g., sputum, cerebrospinal fluid, pus). Tubercle bacilli may be cultured; however, cultures may take up to six weeks. Cultures will allow performing tests for antibiotic susceptibility.
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**Treatmen**
Treatment for latent TB is generally nine months of isoniazid. Treatment for active TB should be consistent with the World Health Organization DOTS protocol. Incomplete treatment can lead to *M. tuberculosis* becoming resistant, therefore adherence to therapy is important to prevent treatment failures.

**Infection prevention and control measures**
IPC measures include; engineering controls, administrative controls, and personal protective equipment. Engineering controls involve negative pressure isolation rooms, enhanced ventilation, ultraviolet irradiation, or high efficiency particulate air filtration systems. Sunlight is a good source of ultraviolet rays; if no other measures are available – open the windows. This also provides room ventilation; diluting out bacteria in the air.

Administrative controls include identifying patients with signs and symptoms of TB, isolation of suspected cases, and prompt treatment of active cases. Personal protective equipment that can be used to limit transmission includes the use of a surgical mask for symptomatic patients, especially if they leave their room, and the use of N-95/FFP masks for healthcare workers. If these masks are not available, then surgical masks should be used.

**Conclusion**
Despite the immense global impact of TB, it is treatable and preventable. Occupational exposure remains a significant risk to healthcare workers everywhere. IPC measures are important to lessen exposure of staff and patients.

**SECTION B: Antibiotic Resistant Microorganisms**

**Introduction**
Antimicrobial agents have been used since the 1940s, greatly reducing illness and death from infectious diseases. However, many microorganisms have developed resistance to antimicrobials, making them less effective. People infected with resistant microorganisms have longer and more expensive health care stays and are more likely to die from infection. Resistant microorganisms have a world-wide distribution and are a cause of major concern.
Methicillin-resistant *Staphylococcus aureus* (MRSA)*^{6,10}*

**Background**

*Staphylococcus aureus* is a Gram-positive coccus and a leading cause of infection. Up to 30% of people are colonised in the nose, pharynx or perineum, and may become transiently colonised on the hands. Colonisation, especially of intact skin, is harmless, however it can increase the risk of infection, and carriers may transmit infection to others.

**Mechanisms of resistance**

*S. aureus* can become resistant to antibiotics, especially penicillins and cephalosporins. Methicillin, although no longer used for treating infections, is used to test for this resistance; therefore the strains are called ‘methicillin-resistant’ (MRSA). The resistance is due to an altered bacterial cell wall, which has lost the ability to bind to the antibiotics, therefore MRSA bacteria are resistant to virtually all penicillins and cephalosporins.

**Epidemiology**

MRSA first became a problem in the 1960s; today it has reached epidemic proportions. Globally, the burden of disease caused by healthcare-associated and, more recently, community-associated MRSA, is rising. This has resulted in considerable health care pressures due to increased lengths of stay, costs, morbidity, and mortality. Although rates vary from country to country, and even from hospital to hospital, MRSA is the commonest antibiotic-resistant pathogen in hospitals.

**Community-associated MRSA**

Until recently, MRSA was considered to be primarily healthcare-associated (HA-MRSA), affecting older adults with co-morbidities. Recently, community-associated MRSA (CA-MRSA) has emerged in many parts of the world. In contrast to HA-MRSA, CA-MRSA occurs in healthy individuals. Acquisition of CA-MRSA is associated with crowding, compromised skin integrity, contaminated items or surfaces, and lack of cleanliness. The introduction of CA-MRSA strains into health care settings is a major concern.

**Control measures**

See Table 8.1-Major Pathogens of Concern in Healthcare Facilities for MRSA control measures.
Vancomycin-Resistant Staphylococcus aureus (VRSA)
Vancomycin is the drug of choice for treatment of MRSA infections. Of concern is the appearance of S. aureus with a reduced susceptibility to vancomycin (called VRSA), which is MRSA containing the resistance genes Van-A or Van-B. Spread of these strains has a potential for major public health consequences. VRSA appeared in Japan in 1996, then in the United Kingdom, Asia, Brazil, US and France. Strict adherence to Contact Precautions and additional precautions are required for patients carrying these microorganisms.

Vancomycin Resistant Enterococcus (VRE)

Background
Enterococci are facultative anaerobic Gram-positive cocci that are part of the normal gut flora but may be present in the oropharynx, vagina, or skin. Enterococci can also be found on environmental surfaces. These bacteria can cause serious infections, such as septicemia, endocarditis, urinary tract infections, and wound infections, especially in immunocompromised patients.

Infections with enterococci are treated with glycopeptides, for example vancomycin, which block the synthesis of the microbial cell wall. VRE is an Enterococcus that is resistant to vancomycin. There are two types of resistance. Intrinsic resistance, demonstrated by E. gallinarum and E. casseliflavus, is a naturally occurring low-level resistance. These microorganisms are less commonly associated with serious infections and are not associated with outbreaks. The second type is acquired resistance which occurs in E. faecium and E. faecalis. These are the commonest cause of serious VRE infections and carry resistance genes, with Van-A and Van-B being the most clinically relevant.

Epidemiology
VRE was first isolated in Europe in the 1980’s. Since then, reports of VRE colonisation and infection have rapidly increased and outbreaks have occurred globally. According to European Antimicrobial Resistance Surveillance System (EARSS) data from 2008, in some European countries VRE are found in almost 30% of invasive Enterococcus infections. However, Denmark and the Netherlands have managed to keep rates at or close to zero by enforcing stringent IPC policies.
Clinical significance
Infection with VRE is hard to treat and is associated with high patient mortality rates, prolonged hospital stay, and increased cost of care. Recent reports of transfer of the Van-A gene from vancomycin-resistant *E. faecalis* to MRSA (leading to VRSA), raise concerns that the spread of VRE is creating a reservoir for mobile resistance genes. There is now the threat of large scale emergence of VRSA to add to the global crisis of antimicrobial resistance.

Acquisition and transmission
Patients who are colonised carry VRE as part of their gut flora and demonstrate no symptoms. However, they may act as a reservoir for spread. The length of time a patient remains colonised is variable. VRE is spread by direct contact via the hands of healthcare workers or indirectly through contaminated materials or equipment. The environment plays a large role in its spread because VRE can survive on inanimate objects for weeks. Proper cleaning and disinfection of surfaces and shared equipment is extremely important in preventing transmission. Equipment that may normally be shared between patients, such as thermometers and blood pressure cuffs, should be dedicated to individual VRE positive patients, if possible.

Laboratory testing methods
Accurate and early detection of colonisation or infection is important to initiate precautions and prevent the spread of VRE. Diagnosis is usually made by microbial culture or by molecular methods, such as polymerase chain reaction (PCR) assays.

Control measures
See Table 8.1 for Management of Major Pathogens of Concern in Healthcare Facilities for control measures.

*Clostridium difficile* infection

**Background**
The prevalence of *Clostridium difficile* infection (CDI) and number of outbreaks has been increasing globally for the past 10 years. CDI primarily occurs in patients who are exposed to antibiotics in health care facilities. It may cause uncomplicated diarrhoea, pseudomembranous colitis, and, on rare occasions, ileus or toxic megacolon.
Pathology

*Clostridium difficile* is a Gram-positive spore-forming anaerobic bacillus; it is widely distributed in the environment. The vegetative form is the active state when the microorganism produces toxins and can be killed by antibiotics. The spore form is the dormant state and does not produce toxins. Spores are resistant to many types of disinfectants, heat, and dryness and can persist in the environment for months on bed rails, commodes, electronic thermometers, stethoscopes, and skin folds.

Some strains of CDI produce two cytotoxins (Toxin A, Toxin B) which bind to receptors on intestinal epithelial cells causing inflammation and diarrhoea. Both toxins appear to be cytotoxic and enteropathic. Exposure to antibiotics, such as clindamycin, penicillins, cephalosporins, and fluoroquinolones, alters the gut flora and seems to be an important risk factor for CDI. Mild disease is characterised by non-bloody diarrhoea that is often mucoid and foul smelling, cramping, nausea, dehydration, low grade fever, and leukocytosis. Severe disease can include colitis, watery diarrhoea, abdominal pain, fever, nausea, abdominal distension, and pseudomembranes in the gut.

New strain

Since 2000 there has been an increase in the incidence of the BI/NAP1/027 strain of *C. difficile*. This strain causes a severe illness, and is more resistant to standard therapy, more likely to relapse, and associated with higher mortality. The strain produces approximately 16 times the amount of toxin A and 23 times the amount of toxin B than normal strains because of the partial deletion of a gene.

Colonisation

Approximately 3-5% of healthy adults and 20-40% of hospitalised patients may be colonised with inactive spores of *C. difficile*. Colonised patients are generally not symptomatic; however they may be a potential reservoir for transmission. Evidence suggests that spores on the skin of asymptomatic patients can contaminate the hands of healthcare workers. There are no recommendations to treat carriers.

Control measures

Many measures have been used to prevent spread of *C. difficile* (See Table 8.1). Other measures include the discontinuation of all antibiotics upon
suspicion of CDI and facility-wide antibiotic control policies. Prompt notification of patients with diarrhoea to the IPC personnel can assist in focusing interventions.

Although effective against vegetative bacteria, alcohol-based hand hygiene products may be less effective against the *C. difficile* spore than soap and water. Environmental audits can assist in identifying sources, such as multiuse patient care equipment, that can be targeted for cleaning. Strict adherence to cleaning the environment is important. Sporicidal agents should be used for cleaning, especially during outbreaks; these include various formulations of hydrogen peroxide and chlorine-based products like bleach. Routine identification of asymptomatic carriers or repeat testing after treatment is not recommended.

**Multi-drug resistant Gram-negative microorganisms**

**Microorganisms of concern**

*Enterobacteriaceae (Escherichia coli and Klebsiella pneumoniae)*

Enterobacteriaceae are a large group of fermentative bacilli that are a normal part of the gastrointestinal flora. They are among the most common isolates from inpatients. The common cause of resistance is the production of beta-lactamases, enzymes which destroy some of the penicillin and cephalosporin antibiotics. *Serratia* and *Enterobacter* species may also be multi-drug resistant.

*Acinetobacter species*

*Acinetobacter* is a non-fermenting bacterium that is present in aquatic environments in nature. It is an opportunistic pathogen for humans and may cause healthcare-associated infections (HAI), especially ventilator-associated pneumonia (VAP), bacteraemia, and urinary tract infections (UTI).

*Pseudomonas aeruginosa*

*P. aeruginosa* is a non-fermenting bacterium that is ubiquitously present in aquatic environments in nature; it is resistant to many antibiotics. It can be an opportunistic pathogen for humans and a major cause of HAIs. *P. aeruginosa* is responsible for a wide range of severe infections including VAP, bacteraemia, and UTI.
Mechanisms of resistance and epidemiology

There are many mechanisms of resistance associated with Gram-negative bacteria and these microorganisms often use multiple mechanisms against the same antibiotic. Gram-negative bacteria are efficient at acquiring genes that code for antibiotic resistance, especially in the presence of antibiotic pressure.

*E. coli* and *Klebsiella* species can have extended spectrum beta-lactamase (ESBL) enzymes that are plasmid-mediated (plasmids are small pieces of genetic material that are independent and can be transferred between bacteria) so the genes encoding these enzymes are easily transferable among different bacteria. ESBL enzymes cause resistance to most beta-lactam antibiotics, penicillins, cephalosporins, cephemycins, carbapenems, and monobactams. ESBLs are often located on large plasmids that harbour resistance genes for other antimicrobial classes such as aminoglycosides and fluoroquinolones.

ESBLs were first detected in Europe in 1983. There are several types of ESBLs, including TEM, SHV, and CTX-M. ESBLs had originally mainly been of the TEM and SHV types, mostly found in *K. pneumoniae*, and at times associated with institutional outbreaks. More recently, *E. coli*-producing CTX-M enzymes have emerged worldwide as a cause of community-onset UTI and bloodstream infections.

The prevalence of ESBL-producing strains varies by geography, type of facility, and patient age. SENTRY Antimicrobial Surveillance data showed that the rate of ESBL-producing strains of *Klebsiella* species in bloodstream infections between 1997 and 2002 was 43.7% in Latin America, 21.7% in Europe, and 5.8% in North America. The SMART Program (Study for Monitoring Antimicrobial Resistance Trends) reported high rates of ESBL-producing *E. coli* in China (55%) and India (79%) of *E. coli* isolates in 2007.

Carbapenem antibiotics are the treatment of choice for serious infections due to ESBL-producing microorganisms; however, unfortunately, carbapenem resistant isolates have also been reported. Carbapenem-resistant Enterobacteriaceae (CRE) have been identified in many parts of the world; outbreaks have also been documented. *Klebsiella pneumoniae* carbapenemase (KPC) producers are a major problem in the United States, Greece, and Israel. VIM metallo-carbapenemases have also been identified.
in *K. pneumoniae* in Greece. Recently, a new carbapenemase, New Delhi metallo-beta-lactamase 1 (NDM-1), has been discovered in patients in India and Pakistan.

**Clinical significance**
Patients with Gram-negative multi-drug resistant infections have increased length of stay and increased infection-related health care costs. Initial antimicrobial therapy is often less successful, leading to greater morbidity and mortality.

**Control measures**
See Table 8.1 Major Pathogens of Concern in Healthcare Facilities for control measures.

**Management of Pathogens in Low Resource Countries**

IPC management of these various pathogens differs depending on the institutional setting and the resources available. At a minimum, hand hygiene should be a focus in all health care institutions. Healthcare workers should clean their hands before and after contact with patients or the patients’ environment. This is the single most important control measure. Transmission-based precautions depend on the particular pathogen, especially in an acute care setting or during an outbreak. Patients colonised or infected with a particular pathogen may be placed in a single room or cohorted (roomed in) with other positive patients.

**Conclusion**

Antimicrobial resistance is a world-wide public-health problem whose solution is multifaceted. Improving the behaviours of prescribers, dispensers, and consumers is essential. Global awareness of the issue of resistance and surveillance for significant pathogens in the parts of the world where these pathogens are prevalent are primary considerations. Integration of antimicrobial stewardship processes may be beneficial. Implementation of appropriate IPC practices will help to reduce the spread of these microorganisms.
Table 8.1. Management of Major Pathogens of Concern in Healthcare Facilities

<table>
<thead>
<tr>
<th></th>
<th>MRSA*</th>
<th>VRE*</th>
<th>MDRGN*</th>
<th>CDI*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients at Risk</strong></td>
<td>Previous antibiotic use, severe underlying illness, prolonged hospital stay, previous contact with medical facility, use of invasive procedures, close proximity to a patient that is colonized or infected with MRSA</td>
<td>Previous antibiotic use, severe underlying illness, prolonged hospital stay, previous contact with medical facility, use of invasive procedures, close proximity to a patient that is colonized or infected with VRE</td>
<td>Previous antibiotic use, severe underlying illness, prolonged hospital stay, previous contact with medical facility, contact with a facility with known outbreaks with MDRGN microorganisms</td>
<td>Previous antibiotic use, severe underlying illness, prolonged hospital stay, advanced age, gastrointestinal surgery/manipulation, history of irritable bowel disease, patients on proton pump inhibitors</td>
</tr>
<tr>
<td><strong>Admission Screening Sites</strong></td>
<td>Yes, based on patient risk factors, swab of nares, rectal, wounds, exit sites</td>
<td>Yes, based on patient risk factors, rectal swab</td>
<td>Based on local epidemiology and patient risk factors, rectal swab</td>
<td>No</td>
</tr>
<tr>
<td><strong>Route of Transmission</strong></td>
<td>Contact (plus droplet for symptomatic patients with pneumonia)</td>
<td>Contact (plus droplet for symptomatic patients with pneumonia)</td>
<td>Contact</td>
<td>Contact</td>
</tr>
<tr>
<td><strong>Isolation Precautions?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Pathogens Important to Infection Prevention and Control

<table>
<thead>
<tr>
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<th>MDRGN*</th>
<th>CDI*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Documentation</strong>&lt;br&gt; (flagging of patients)</td>
<td>It may be of benefit to implement a system to designate patients known to be colonised or infected with antibiotic resistant microorganisms for early notification on readmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Environmental Cleaning</strong></td>
<td>Routine cleaning with attention to high touch surfaces</td>
<td>Routine cleaning with attention to high touch surfaces</td>
<td>Routine cleaning with attention to high touch surfaces</td>
<td>Routine cleaning with attention to high touch surfaces and the use of a sporicidal agent</td>
</tr>
<tr>
<td></td>
<td>Consider double cleaning in outbreak situations</td>
<td></td>
<td></td>
<td>Consider double cleaning for outbreak situations</td>
</tr>
<tr>
<td><strong>Discontinuation of Precautions</strong></td>
<td>This is an unresolved issue</td>
<td></td>
<td></td>
<td>No diarrhoea for at least 48 hours</td>
</tr>
<tr>
<td></td>
<td>Some institutions use the following criteria: Negative results from all colonised/infected body sites - 3 consecutive negative cultures taken at least one week apart in the absence of antibiotic therapy</td>
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<tr>
<td></td>
<td>Note:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Recolonisation is known to occur; on-going monitoring is recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Consider maintaining isolation precautions in an outbreak setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up of Contacts</strong></td>
<td>Two sets of specimens taken on different days, with one taken a minimum of 7 days after last exposure, especially in an outbreak setting</td>
<td>Based on local epidemiology and patient risk factors</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>
**IFIC Basic Concepts of Infection Control**

*MRSA = methicillin-resistant S. aureus; VRE = vancomycin-resistant Enterococcus; MDRGN = Multi-drug resistant Gram-negative microorganisms; CDI = C. difficile infection*

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<th>MDRGN*</th>
<th>CDI*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Point Prevalence</strong></td>
<td><strong>In an outbreak setting:</strong></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Conduct serial (e.g., weekly) unit-specific point prevalence culture surveys of the target antibiotic-resistant microorganism to determine if transmission has decreased or ceased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Environmental Cleaning</strong></td>
<td>Routine cleaning with attention to high touch surfaces</td>
<td>Routine cleaning with attention to high touch surfaces</td>
<td>Routine cleaning with attention to high touch surfaces</td>
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<td></td>
<td></td>
<td>Consider double cleaning in outbreak situations</td>
<td></td>
<td>Consider double cleaning for outbreak situations</td>
</tr>
<tr>
<td><strong>Additional Outbreak Measures</strong></td>
<td></td>
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<tr>
<td></td>
<td>Strict cleaning of multi-use patient equipment in between patients</td>
<td>Dedicated patient equipment to positive cases</td>
<td>Education of staff, patients, and visitors</td>
<td>Auditing of outbreak unit/area including hand hygiene, isolation precautions practices, and environmental cleaning</td>
</tr>
</tbody>
</table>

*MRSA = methicillin-resistant S. aureus; VRE = vancomycin-resistant Enterococcus; MDRGN = Multi-drug resistant Gram-negative microorganisms; CDI = C. difficile infection*
References


15. Peleg A, Hooper D. Hospital-Acquired Infections Due to Gram-
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Further Reading


