Multiresistant Microorganisms and Infection Control

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Multidrug-resistant microorganisms (MDRO) are bacteria that are insensitive to the mode of action of most antibiotics [1]. Bacteria has the ability not only to modify themselves to resist antimicrobials but also to propagate these resistance traits and even share resistance genes with other contemporary bacteria within their environment, enabling them to overcome host strategies aimed against them. This microorganisms' resistance is a biological property that is defined in the genome of the microorganisms and is passed on in their multiplication. The use of antibiotics for decades has eventually led to the selection of bacterial strains that are resistant to a range of drugs. Thus, even sensitive bacterial strains could be displaced.

Bacteria may use four major bacterial resistance strategies in order to disrupt the essential steps required for the effective action of the antimicrobial agents:

1. By prevention of the antimicrobial from reaching its target by reducing its ability to penetrate into the cell
2. By expulsion of the antimicrobial agents from the cell via general or specific efflux pumps
3. By inactivation of antimicrobial agents via modification or degradation
4. By modification of the antimicrobial target within the bacteria

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E. Presterl et al. (eds.), *Basic Microbiology and Infection Control for Midwives*,
https://doi.org/10.1007/978-3-030-02026-2_11

No single mechanism of resistance is considered responsible for the observed resistance in a bacterial organism, but several different mechanisms may work together to confer resistance to a single antimicrobial agent.

MDRO are a serious health problem in all healthcare facilities. Multidrug-resistant microorganisms are present not only in hospitals but also in rehabilitation centres, long-term care facilities, medical practices, etc. What is most alarming today is the rate at which antibiotic resistance often develops and how quickly it spreads across the globe and among different species of bacteria. In addition, no European country can claim to be unaware of the problem of MDRO. It is crucial to promote healthcare with high-quality standards, thereby reducing the risk of MDRO and limiting their spread through control measures.

The majority of all infectious agents in the EU are accounted for by the nosocomial pathogens. An estimated 4 million people a year in Europe acquire a nosocomial (= hospital-acquired) infection, of which approximately 80,000 die from it. Here, MDRO represent an increasing danger due to the limited therapeutic spectrum due to their multiresistance behaviour (Table 11.1).

In 2017 the World Health Organization has grouped the pathogens according to the species and the type of resistance and then stratified the results in three priority tiers: critical, high and medium:

1. Critical
   - *Acinetobacter baumannii*, carbapenem-resistant
   - *Pseudomonas aeruginosa*, carbapenem-resistant

Table 11.1 Relevance and transmission of multidrug-resistant microorganisms

Effective hygiene measures		
Microorganism	Transmission	Relevance
ESBL (extended-spectrum β-lactamase producers CAR (carbapenem-resistant Gram-negative rods) MDRGN (multidrug-resistant Gram-negative microorganisms)	*Direct*: hands *Indirect*: contact with pathogen-containing secretions, stool, wounds, contaminated objects	• Often asymptomatic carriers • Mostly Gram-negative microorganisms • Occurrence as an endogenous infectious agent in the intestine → Eradication not possible
MRSA (methicillin-resistant *Staphylococcus aureus*)	*Direct*: hands, from skin to skin (dandruff) *Indirect*: contaminated objects	• Healthcare-associated infections, i.e. sepsis, pneumonia, urinary tract infections, surgical site infections • Eradication possible!
VRE (vancomycin-resistant enterococci)	*Direct*: hands, from skin to skin *Indirect*: contaminated objects	• Healthcare-associated infections • There are healthy carriers (intestinal microorganisms) • → Eradication not possible • High mortality by infections

   - *Enterobacteriaceae*, carbapenem-resistant, 3rd-generation cephalosporin-resistant
2. High priority
   - *Enterococcus faecium*, vancomycin-resistant
   - *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and vancomycin-resistant
   - *Helicobacter pylori*, clarithromycin-resistant
   - *Campylobacter*, fluoroquinolone-resistant
   - *Salmonella* spp., fluoroquinolone-resistant
   - *Neisseriagonorrhoeae*,3rd-generationcephalosporin-resistant,fluoroquinolone-resistant
3. Medium priority
   - *Streptococcus pneumoniae*, penicillin-non-susceptible
   - *Haemophilus influenzae*, ampicillin-resistant
   - *Shigella* spp., fluoroquinolone-resistant

The most important MDRO in healthcare settings are:

- MRSA (methicillin-resistant *Staphylococcus aureus*)
- ESBL (extended-spectrum β-lactamases) producers *Enterobacteriaceae*/ MDRGN (multidrug-resistant Gram-negatives)
- VRE (vancomycin-resistant enterococci)

11.1 Methicillin-Resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains have been known since 1961. Since 1975, a worldwide increase of MRSA has been observed. The frequency of MRSA is regional but also varies from hospital to hospital and from department to department. Increased MRSA occurrence may be indicative of inadequate sanitary measures and is associated with therapeutic problems and increased costs. The incidence of MRSA increases with the size and specialties of a hospital, as well as with the severity of the underlying diseases of the patients. MRSA strains are not only resistant to methicillin and oxacillin but also to all other β-lactam antibiotics (penicillins, cephalosporins, carbapenems).

Infections with MRSA are a serious medical problem. They usually affect critically ill people who are impaired in their defence and thus contribute to increased infectious morbidity and mortality in this patient group. Although from a clinical perspective, the mere colonization with MRSA has a much lower relevance compared to the infection, it is important for the retransmission to determine whether an infection or just colonization exists. Hospital hygiene measures designed to prevent transmission of MRSA to other patients are therefore equally applicable to infected as well as populated patients. As in the case of the spread of other multidrug-resistant microorganisms, the emphasis is on compliance with basic hospital hygiene measures (hand hygiene, protective clothing, supply and disposal, reprocessing of medical devices).

Staphylococcus aureus can survive very well in inanimate environment, in dust and in dry conditions; therefore, the pathogen is predestined as a hospital microorganism. In humans, it occurs in the nose, throat and perineum. About 1/3 of the normal population is carrier of the microorganisms. This is colonization, not infection. Especially wounds, eczema and ulcers (or decubitus ulcers) are susceptible to infections with *S. aureus*. Most of the infections caused by *S. aureus* usually develop endogenously, that is to say via autoinfection through the pre-existing microorganisms' colonization on the body. In Austria about every 10th, *S. aureus* is an MRSA. Approximately 30–40% of patients colonized with MRSA develop infection by previous colonization. Most infections occur locally superficial on the skin in the form of (soft tissue) abscesses, folliculitis, cellulitis, carbuncles or wound infections. In rare cases, *S. aureus* can also trigger deep processes, e.g. pneumonia with multiple abscesses. In new-borns and infants, *S. aureus* may in rare cases be the cause of SSSS (staphylococcal scalded skin syndrome) (also called *dermatitis exfoliativa neonatorum Ritter von Rittershain*, Ritter's disease for short). This is a rare staphylococcal skin infection that causes haematogenous spread of staphylococcal toxins to cause skin detachment that is fatal if left untreated.

The *transmission* of MRSA is primarily by contact (*hands*, instruments, dressings, clothing, work surfaces), if usual, general hygiene measures are not sufficiently observed. Person-to-person transmission primarily occurs through the hands of the staff after contact with colonized/infected MRSA patients.

A nasal colonization of staff with MRSA is usually temporary. With permanent nasal colonization, the risk of colonization of the hands and thus transmission to patients is increased, whereby the risk of colonization is increased in personnel with dermatitis or skin lesions.

In special cases, microorganisms are also strongly released into the ambient air and spread. This includes patients with massive colonization or respiratory infection, large MRSA-colonized wound areas (e.g. burn victims) or MRSA-populated, scaly skin diseases. Such patients (= spreaders) must be strictly isolated (single room), and the caring staff (as well as relatives, visitors) must wear complete protective clothing in the *isolation room*.

Protective equipment by MRSA: Gloves, disposable plastic apron, long-sleeved disposable gown with cuffs, face mask.

Duty to inform: It is important to ensure that all employees in one area (doctors, carers, physiotherapists, cleaners) are aware of both the patients concerned and the appropriate hygiene measures. Everyone needs to know about the MRSA status of the patient so that appropriate precautions can be taken (protective equipment). Visitors to the patient must also be informed about hygiene measures before and after entering the patient room.

Screening: In principle, MRSA screening should only be performed in patients with specific evidence or suspicion of colonization/infection. The *primary screening is done via a nose/throat swab* or (in previously known positive patients) from the former positive localization (wounds, secretions, etc.). Patients who meet a certain risk profile (see Risk Factors) are primarily screened.

Risk factors for colonization/infection with MRSA in the hospital:

- Previous KH stay
- Length of the KH stay
- Previous antibiotic therapy
- Use of catheters, drains, etc.
- Surgical intervention (wounds)
- Decreased immune system (oncological patients, intensive care patients, etc.)
- Other patients with MRSA (cohabitation)
- Poor compliance regarding hygiene measures
- Admission from countries with a high rate of MDRO

Therapy MRSA can be effectively eliminated in asymptomatic carriers by eradication. These are local applications in the nose (mupirocin, chlorhexidine), on colonized wounds and on the colonized skin (daily antiseptic wash or baths with chlorhexidine, PVP iodine soap). Systemic MRSA eradication is not intended for prophylaxis or rehabilitation and is indicated only in rare cases. The resistance behaviour of the microorganisms eliminates all β-lactam antibiotics as a therapeutic option!

Hygiene measures:

- *Hand disinfection* after contact with patients or with objects close to the patient (even after the gloves have been removed)
- Single room (desirable, absolutely necessary for spreaders)
- Gloves (for all actions at the place of infection/settlement)
- Protective equipment (with spreaders, plastic apron, protective coat, face mask)
- Use used bandage material, laundry, used instruments, etc. without interim storage or contact with objects in the disposal bag or transport container
- Daily maintenance disinfection of the patient room
- Obligation to inform employees, the patient and the visitors

Proof of MRSA should definitely be documented in the medical history and in the doctor's brief!

11.2 Multidrug-Resistant Gram-Negative Bacteria

The term ESBL (extended-spectrum β-lactamases) refers to an enzyme that cleaves β-lactam rings, thereby rendering an important group of antibiotics, the β-lactam antibiotics, ineffective. Most commonly, these enzymes are found in Gram-negative bacteria of the *Enterobacteriaceae*, which live in the gut. Thus, those bacterial strains having this enzyme are *referred to as ESBL producers* (e.g. *E. coli* ESBL). Gram-negative bacteria have built-in abilities in the last decades to find new ways to

be resistant: they can pass along genetic materials that allow other bacteria to become drug-resistant as well. Multidrug-resistant Gram-negative (MDRGN) bacteria are a type of Gram-negative bacteria that are resistant to more than one drug in three or more antimicrobial drug classes (acylureidopenicillines, cephalosporins, quinolones, carbapenems). The increasing incidence of serious infections due to antimicrobial drug-resistant Gram-negative bacteria has increased, and MDRGN strains of *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* have become of most concern because they have been reported by hospitals all around the world. Infections with these microorganisms are very difficult to treat and can lead in some cases to death of up to 50% of the infected patients.

Since carbapenems are so far the last choice against infections caused by ESBL producer bacteria, last decade increase in carbapenem resistance rates, together with the lack of newly emerging antimicrobial drugs, has resulted in the revisit of old antibiotic drugs such as colistin and fosfomycin and carbapenem-resistant strains which represent nowadays a significant threat to public health. These bacteria have the potential for widespread transmission of resistance via mobile genetic elements; while some strains are innately resistant to carbapenems, others contain mobile genetic elements (i.e. plasmids) that result in the production of carbapenemase enzymes (carbapenemases), which break down most β-lactam antibiotics, including carbapenems. These carbapenemase-producing genes are frequently co-located on the same mobile element with other resistance genes, which can result in co-resistance to many other antibiotic drug classes and make them difficult to manage.

MDRGN can cause a variety of infections, most commonly urinary tract infections caused by bacteria in the digestive tract, which can easily enter the urinary system due to their anatomical proximity. Other common infections are respiratory infections (pneumonia), wound infections (postoperative) and sepsis. A colonization of the intestine with MDRGN pathogens can be quite asymptomatic and is harmless for the person concerned. Due to the fact that most bacteria living in the intestine are Gram-negative, a complete eradication of MDRGN pathogens in affected individuals is not possible. Thus, the spread of the pathogens is prevented solely by hygienic measures.

Like all other hospital microorganisms, the transmission of MDRGN pathogens takes place *via direct contact* (Stool!) or *indirectly via contaminated objects* (patient environment, instruments, laundry, care utensils, sanitary facilities, etc.). Even asymptomatic carriers represent a source of infection (stool, anogenital area)!

Risk factors' colonization with ESBL/MDRGN microorganisms:

- Previous antibiotic therapy
- Previous hospital stays (including length of stays)
- Immunosuppression after organ transplantation
- Invasive aids (catheters, drains, intubation, probes)
- Stay in an intensive care unit (including neonatology and haematology-oncology stations)
- Surgical procedures or wounds

- Severe underlying disease or comorbidities
- Stay in a hospital abroad

The preventive measures for MDRGN agents are defined as bundles. Primary is to ensure compliance with the *standard infection control measures* (*five moments of hand hygiene*, *aseptic operation*, *protective clothing where required*, *compliance of the staff*). In patients who are a source of litter (urinary/faecal incontinence, open wounds, scaly skin diseases, severe cough, lack of compliance), isolation in a single room (with its own toilet) is essential. Colonized patients who do not represent a source of scattering should be evaluated according to the situation. A cohort of populated patients is quite possible but in consultation with hospital hygiene.

Further strong recommended infection control measures by MRGN:

- Contact precautions
- Implementation of multimodal IPC strategies
- Surveillance of MDRGN infection and surveillance cultures for asymptomatic CRE colonization
- Environmental cleaning

Measures in isolated MDRGN carriers: Single room with own toilet, long-sleeved disposable gown with cuffs, face mask and gloves for all actions in the isolation room, co-ordination in consultation with hospital hygiene.

Therapeutic indication: Colonization with MDRGN pathogens without clinical signs of infection is not an indication for antibiotic therapy. An eradication scheme is currently not established. In some cases, a wash with an antiseptic washing lotion to reduce the superficial colonization of the skin (after consultation with the hospital hygiene) is considered. Due to the high probability of reinfection with the own enterobacteria, therapy/eradication in asymptomatic MDRGN carriers is not meaningful or not feasible.

Screening: Screening is only to be carried out if there is a corresponding suspicion (see Risk Factors). Primary screening in high-risk patients is done by smears from the stool or by rectal swab. Depending on the clinical manifestation (urine, wounds, bronchial secretions), the smear may be taken at the infected body site if there are signs of inflammation. Patients of a newly discovered MDRGN carrier should in principle always be screened.

Proof of ESBL/MDRGN should definitely be documented in the medical history and in the doctor's brief!

11.3 Vancomycin-Resistant Enterococci

Vancomycin-resistant enterococci (VRE) are colonies of bacteria that are resistant to the antibiotic vancomycin and thus can only be treated with reserve antibiotics. Enterococci are part of the physiological intestinal flora in humans and are considered to be only conditionally pathogenic. Clinically, *E. faecalis* and *E. faecium* are

the most important. Enterococci are very environmentally stable and form numerous resistances to antibiotics. In *E. faecium*, e.g. can be expected with an ampicillin resistance in 90% of cases. Resistance to glycopeptide antibiotics (e.g. vancomycin or teicoplanin) has also increased in recent years, resulting in the nomenclature of VRE. As with MDRGN microorganisms, gut rehabilitation is not possible with VRE, which is why intestinal colonization with VRE can persist for a long time (months, even years).

VRE do not cause *any pathogen-specific symptoms* that can be used to make a diagnosis. VREs are recognized by the presence of enterococci in clinically relevant test materials and the resistance to vancomycin in the antibiogram. Local infections caused by VRE are often difficult to treat due to vancomycin resistance, which is why this bacterial group is one of the healthcare-associated infections. In particular, VRE causes infections of chronic wounds such as decubitus, urinary tract infections in indwelling catheters or the respiratory tract in artificial respiration and tracheostomy and in severe cases also sepsis. Of course, the symptoms depend solely on the location and severity of the infection.

The *transmission* from person to person is mostly by contact over the hands (with stool) as well as over contaminated objects or near-patient surfaces. Contamination of the environment is at, e.g. open wounds possible (stray sources). Since enterococci are environmentally stable, disinfection measures in the hospital (hand, instrument, surface disinfection) are of great importance.

Risk factor colonization with VRE microorganisms:

- Immunosuppression
- Severe underlying disease or co/multi-morbidity
- Surgical procedures or open wounds
- Invasive aids (catheters, drains, intubation)

As in the case of MDRGN and MRSA, a *screening* for VRE is only carried out on suspicion based on the risk profile and in addition, when receiving known VRE carriers (from previous or previous examinations), with fellow patients of a VRE carrier.

Therapeutic indications: Colonization with VRE without clinical signs of infection does not constitute an indication for antibiotic therapy. An eradication scheme (with topical agents) is currently not indicated.

11.4 Hygiene Measures with Vancomycin-Resistant Enterococci

- Hand hygiene:
  - Personnel: hand disinfection before and after each patient contact (five moments of hand hygiene) and also between cohorted VRE patients
  - Patient: hand disinfection after the toilet visit, after contact with excreta and before leaving the room

  - Visitors: Hand disinfection before and after contact with other patients and before leaving the room
- Single room isolation.
- Own toilet always necessary!
- Co-patients stay in the room until the primary screening and have their own toilet. With VRE freedom they can be moved out of the room.
- Protective clothing (gloves and apron for all medical and nursing activities on the patient).
- Use all utensils only for the patient and wipe them after use.
- Do not take medical documentation with you into the room.
- Routine and targeted cleaning and disinfection of near-patient surfaces.
- Discard waste directly at the patient's bed in closed containers.
- Prepare bowl dishes and urine bottles in the dishwashing unit immediately after use.
- Plan work processes so that activities take place in the "MDRGN room" or at MDRGN providers at the end of the routine (while ensuring good preparation and, if necessary, involvement of a second person to avoid unnecessary interruptions [contamination risk!]).
- Obligation to inform patients, employees in the area, cleaning staff, visitors, etc.

Proof of VRE should definitely be documented in the medical files and in the doctor's letter for the patient!

Further Reading

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