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Infections and Multidrug-Resistant Pathogens in ICU Patients

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Additional information is available at the end of the chapter

Abstract

This chapter aims to highlight the main types of infections in the ICU, in order to improve diagnostic and therapeutic management. Risk factors for patients hospitalised in the ICU will be raised: the increasing use of invasive devices and procedures, aggressive antimicrobial therapies, surgical interventions, immunosuppressive treatments or co-morbidities responsible for immune deficiencies. Starting from the rising mortality risk among patients with hospital-acquired infections (HAI), in the case of failure to control the pathogen in the first 24–48 h, we will tackle about the prevention, reduction and control of the emergence of resistant pathogens. The rational administration of antibiotics will also be addressed, with the aim of reducing adverse reactions, including secondary infections, decreasing the mortality rate, length of hospital stay and costs of health care.

Keywords: ventilator-associated pneumonia, intra-vascular catheter-related bacteraemia, sever sepsis, septic shock, antimicrobial treatment, multidrug resistance

1. Introduction

Modern medicine is a tributary to a continuously increasing degree of diagnostic and therapeutic invasiveness. In particular, intensive care units (ICUs) are confronted with increasing number of patients with marked co-morbidities, severe acute pathology or immune suppression, and intrinsic infectious risk factors. Additionally, given the pathogenicity changes of potentially hospital-acquired pathogens, most healthcare-associated infections (HCAIs) are caused by multidrug-resistant organisms (MDRO).

2. ICU infections

2.1. Severe respiratory infections

Pneumonia is one of the infections frequently requiring hospital admission and urgent anti-microbial treatment due to the risk of rapid evolution to respiratory and multiple organ failure, especially in immunocompromised patients, or when caused by MDRO. The diagnosis of severe pneumonia requires ICU admission given the need for assisted ventilation or oxygen therapy, in the presence of radiological changes, confirming the rapid progression, as well as the evolution towards sepsis [1, 2].

Community-acquired pneumonia (CAP) is caused by bacteria in 85% of cases, the most frequently involved pathogens being *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Severe CAP cases may also be produced by other pathogens (influenza viruses, coronaviruses, Hanta virus, *Legionella*).

Pneumonia may trigger acute myocardial infarction in patients with heart diseases, while in splenectomised patients or with spleen dysfunction, *S. pneumoniae* may cause severe sepsis with lethal outcome within 12–24 h from onset, even under antibiotic therapy.

The treatment of CAP must cover both typical and atypical pathogens. Clinical studies have shown that monotherapy with respiratory fluoroquinolones or tigecycline is almost as effective as therapy with antibiotic associations (ceftriaxone plus doxycycline, azithromycin, or respiratory quinolones) [3].

On the other hand, presently ICUs are especially confronted with respiratory infections acquired during hospitalisation. According to 2012/506/EU European Parliament Decision, hospital-acquired pneumonia (HAP) occurs 48 h or more after admission and was not incubating at the time of admission, while ventilated-associated pneumonia (VAP) arises in 48 h after endotracheal intubation [4]. The microorganisms involved in the aetiology of these pneumonia cases originate in the oropharyngeal or upper airways colonisation flora or by direct inoculation of contaminated solutions, via an endotracheal catheter, or exogenous contamination of respiratory equipment caused by health care staff.

The hospital-acquired risk factors associated with this type of infection are:

- long time sedation,

- general anaesthesia with endotracheal intubation,

- other invasive procedures: bronchoscopy, nasogastric catheterisation,

- prolonged use of assisted ventilation,

- reintubation, change of ventilation circuits at intervals under 48 h,

- post-trauma intubation,

- tracheostomy,

- corticotherapy or other immunosuppressive treatments,

- antibiotic therapy, administration of antacids or H_2 blockers, barbituric therapy after cranial traumas,

- thoracic or upper abdominal surgery,

- emergency surgery,

- administration of over 4 units of blood before the surgical intervention [5, 6].

These factors disturb respiratory functions leading to obstructions, decreased pulmonary volume, decreased filtration of inhaled air, and decreased secretion clearance. The insertion of an endotracheal tube allows the direct access of pathogens into the lower airways or may cause lesions of the epithelial mucosa, which represent breaches. Additionally, inadequate hand hygiene of medical personnel, lack of adherence to universal precautions, errors in decontamination of equipment or in the practice of endotracheal aspiration may favour not only cross-contamination but also the direct access of a massive bacterial inoculum.

This pneumonia is caused by a wide range of pathogens, and it may be plurietiological and is only rarely caused by viruses or fungi. The aetiological agents frequently involved in such infections are not only Gram-negative bacilli (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Escherichia coli*) but also Gram-positive cocci such as *Staphylococcus aureus*. The frequency of MDRO is increasing and influences the treatment, as in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Pseudomonas*, fluoroquinolones, antipseudomonal penicillins and cephalosporins, extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL), *Acinetobacter baumannii*, etc. The risk factors for MDRO infections are the use of antibiotics during the previous 90 days, the onset of pneumonia after 4 days of hospitalisation, circulation of such pathogens in the health care unit in question, as well as the presence of comorbidities (immune suppression or immunosuppressive treatments).

The diagnosis of HAP should be rapidly reached, and the antibiotic treatment has to be promptly introduced, and any delay potentially aggravates the evolution and prognosis. The first antibiotic of choice depends on infection severity, patient's risk factors, and the number of hospitalisation days accumulated until the onset of pneumonia.

The empirical treatment of HAP or VAP occurring during the first five hospitalisation days in patients without risk factors for MDRO must include antibiotics active against not only aerobic Gram-negative bacilli (*Enterobacter* spp., *E. coli*, *Klebsiella* spp., *Proteus* spp., *Serratia* spp.), pathogens with respiratory tropism (*Haemophilus influenzae* and *Streptococcus pneumoniae*), but also methicillin-sensitive *S. aureus* (MSSA). Recommendations include therapeutic schemes based on ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) or ampicillin-sulbactam or ertapenem (**Figure 1**).

In the case of patients with HAP or VAP who are at risk for MDRO infection, regardless of the infection's severity, the antibiotic treatment must be directed against *P. aeruginosa*, *K. pneumoniae* (ESBL-producing strains), *Acinetobacter* spp. and MRSA. Antibiotic associations including antipseudomonal cephalosporins (ceftazidime), an antipseudomonal carbapenem (imipenem) or beta-lactam/beta-lactamase inhibitors (piperacillin-tazobactam), will be administered, in association with antipseudomonal fluoroquinolones (ciprofloxacin) or an
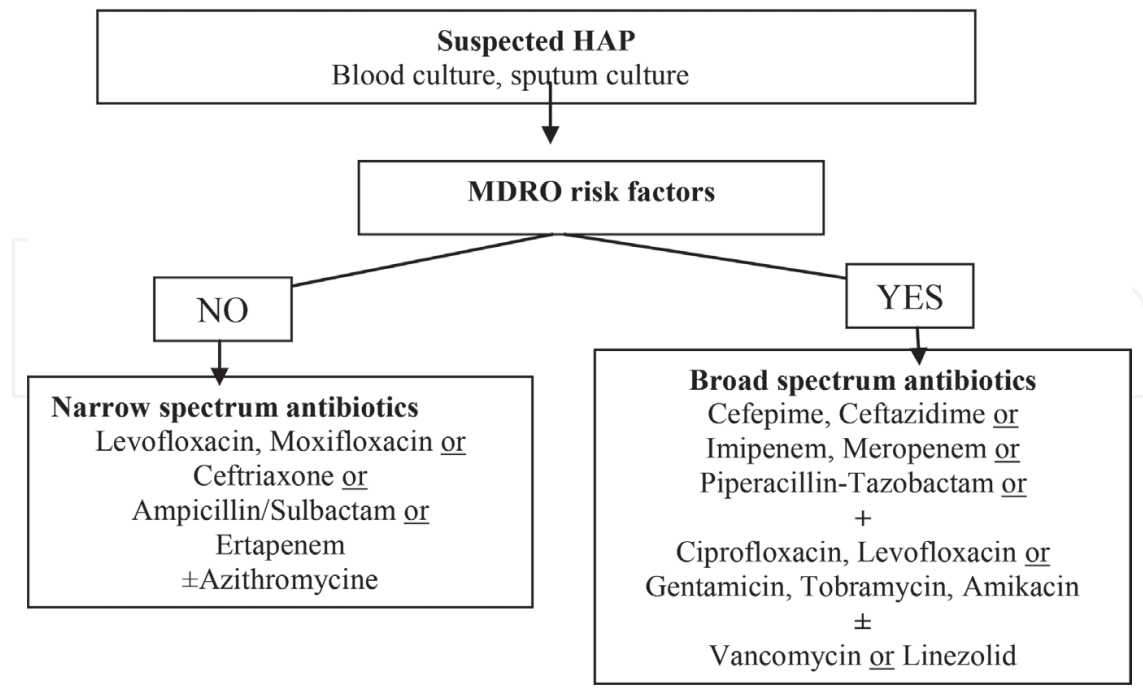
Figure 1. Antibiotic therapy in HAP.

Antibiotic	Adult Doses
Broad-spectrum cephalosporins	
Cefepime	1-2 g every 8-12 hours
Ceftazidime	2 g every 8 hours
Carbapenems	
Imipenem	500 mg every 6 hours or 1 g every 8 hours
Meropenem	1 g every 8 hours
Betalactam/ beta-lactamase inhibitor	
Piperacillin-tazobactam	4.5 g every 6 hours
Aminoglycosides	
Gentamicin	7 mg/kg/day
Tobramycin	7 mg/kg/day
Amikacin	20 mg/kg/day
Fluoroquinolones	
Levofloxacin	750 mg/day
Ciprofloxacin	400 mg every 8 hours
Anti-MRSA antibiotics	
Vancomycin	15 mg/kg every 12 hours
Linezolid	600 mg every 12 hours

Table 1. Empirical antibiotic treatment of HAP with MDRO.

aminoglycoside (tobramycin) and vancomycin or linezolid, to cover MRSA. If a *Legionella* infection is suspected, a macrolide (azithromycin) must also be associated [7] (**Table 1**).

The duration of the antibiotic treatment in HAP must be adjusted to the severity of the disease, the time required to obtain clinical improvement and the aetiological agent, but it has to exceed with at least 3 days the time to clinical improvement. The clinical response occurs after

at least 48–72 h, a period during which the recommendation is to maintain the therapeutic scheme. If, after this interval of empirical treatment, the clinical status of the patient did not improve, the therapeutic scheme must be broadened, potential complications (pleurisy, pulmonary abscess) and/or non-infectious causes must be sought.

2.2. Bacteraemia and septicaemia

2.2.1. Generalised septicaemic infections

The generalised septicaemic infection is an infection with an unpredictable outcome, high severity and increased mortality in the absence of adequate treatment. The correct choice of empirical antibiotic treatment depends on the intelligent use of clinical knowledge and epidemiological and microbiological data regarding the pathology in the area where the patient comes from. The lack of knowledge on the local resistance prevalence is a predictive factor for an incorrect treatment. The basic principle, which guides the treatment of the critical patient, is to rapidly initiate antibiotic treatment at correct doses, concordant with the pharmacokinetic and pharmacodynamic characters of the chosen drug and to adapt the treatment to the changes occurring in the clinical evolution and to the results of the antimicrobial sensitivity tests as soon as these become available.

Immediately after a patient with suspected sepsis is admitted, an attentive anamnesis and a thorough clinical examination are conducted in order to establish the entry and the location of the primary and secondary septic sites. The first emergency microbiological investigations are conducted (repeated blood cultures, cultures from secretions, lesions, urine, sputum, exudates, pleural fluid, etc.) together with evaluations of the renal, hepatic functions and state of consciousness, thus determining the severity of the case [8, 9].

The practical approach includes the emergency admission of the patient into the ICU where prevention or correction of hypovolemia, functional and metabolic dysfunctions are attempted, concomitantly with the prompt initiation of antibiotic treatment according to the maximal probability criterion.

The correct antibiotic treatment targets the resident microbial flora in the organ presumed to be the source of the infectious process.

The empirical treatment of sepsis consists of the association of bactericidal antibiotics with synergistic actions or monotherapy with an ultra-broad-spectrum antibiotic; antibiotics are administered intravenously in order to rapidly achieve an effective concentration in the infection site.

Empirical antibiotic therapy proved to be equally effective in beta-lactam-aminoglycoside associations, monotherapy with carbapenems, broad-spectrum penicillins/beta-lactamase inhibitors (ticarcillin/clavulanic acid, piperacillin/tazobactam) or third- and fourth-generation cephalosporins [10].

The aetiology of sepsis varies with the age of the patient, and the empirical treatment must be adapted to the most probable aetiology, but correlated with age, weight and associated pathology.

Adults with severe sepsis of unknown source must be treated with antibiotics effective against Gram-negative bacilli, *Staphylococcus aureus*, streptococci, respectively carbapenems (meropenem or imipenem) plus vancomycin. Septic shock requires the urgent refilling of the vascular system by infusions with saline solutions until the central venous pressure is re-established (over 80 mm at 6 h from hospital admission); at the same time, the primary source of infection is investigated, blood culture is collected and the first dose of antibiotic is administered, knowing that the time from admission to the initiation of antibiotic therapy is the strongest prognostic factor.

Patients admitted in a state of septic or toxic-septic shock will not be treated with beta-lactam (The bacterial load is very high, the pathogens are in a stationary phase with low protein synthesis, hence with a low synthesis of penicillin-binding proteins, so antibiotics lack their target.)

Colistin has a rapid antibacterial effect completed by a significant post-antibiotic effect against *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*. The most effective administration regimen is at 8 h. Colistin proved an important alternative in the treatment of MDR Gram-negative bacilli. Resistance to colistin is caused by sub-optimal doses. Colistin dosage must be optimised, as this antibiotic is the last option in the treatment of MDRO [11–13].

When a biliary infection is suspected to be at the origin of bacteraemia, the most frequently encountered bacteria are enterococci and aerobic Gram-negative bacilli, which respond well to piperacillin/tazobactam or ticarcillin/clavulanate; alternatively, ceftriaxone, ciprofloxacin or levofloxacin associated to metronidazole may be administered.

A great part (around 25%) of sepsis cases occur as a result of community or hospital-acquired urinary tract infections (UTI), evolving with a renal or complication of prostatic parenchyma. In such cases, the time from hospital admission to the initiation of antibiotic treatment is also decisive for the evolution. After collection of samples for blood and urine cultures, the first dose of broad-spectrum antibiotic active against *E.coli*, *Proteus* spp., *Enterobacter* spp., *Klebsiella* spp., *P. aeruginosa* is administered; more rare cases of sepsis of urinary origin may be caused by Gram-positive bacteria (15%) or by *Pseudomonas* spp., especially in patients with immune deficits. For an effective treatment of community-acquired urosepsis, depending on the type of local susceptibility, a third-generation cephalosporin or a fluoroquinolone may be indicated; in urosepsis following urologic surgery in patients with long-term urinary catheters, the association of a third-generation cephalosporin active against *Pseudomonas* or piperacillin/tazobactam with an aminoglycoside or a carbapenem is useful, this association being required to cover MDRO [14].

It should be noted that treatment in sepsis is complex, antibiotic therapy being accompanied with measures to eradicate the entry site and septic metastases, to correct tissue hypoxia and to maintain hydro-electrolyte and acid-base balance.

2.2.2. Infections associated with invasive devices

Invasive devices (endotracheal, intra-vascular catheters) increase the risk of HCAI especially with MDRO, by colonisation and biofilm formation on the internal surface of these devices. All types of intra-vascular devices may become complicated with blood infections, but arterial

catheters used for the haemodynamic monitoring and peripheral catheters show lower infection risks than central venous caterers (**Table 2**).

The removal of intra-vascular, gastric or bladder catheters, neurosurgical shunts, etc. as soon as they are no longer needed, represents an infection prevention measure. Both their insertion and removal is done by specialised staff, trained to work under sterile conditions, avoiding the risk of contamination. Knowing that invasive devices, catheters included, are the most frequent cause of HCAIs, their insertion must be conducted under aseptic conditions, choosing the most suitable site (for instance, sub-clavian rather than femoral), after ensuring the asepsis of the cutaneous area, preferably with chlorhexidine, and not with alcohol or iodine solutions. In severely immunocompromised patients, the recommendation is to use antibiotic-impregnated catheters. Clinical studies confirm the significant reduction in catheter-associated infections when these are removed as soon as their role is no longer essential [15–17].

An increasing number of patients require central venous catheters for long periods of time (for haemodialysis, total parenteral nutrition, chemotherapy), which favours complications such as thrombosis or infection. Central venous catheter-associated bacteraemia imposes the removal of the catheter and systemic administration of antibiotics. The clinical decision to remove a catheter suspected of infection relies on the presence of local infection signs. The decision to maintain the device is made in the absence of severity signs in patients with technical difficulties of catheter reinsertion in a new site.

There are situations when catheters may not be removed or replaced (lack of venous approach, counter indication of a new intervention, etc.). In such cases, attempts are made to save the venous line by eliminating the intra-luminal colonisation before the onset of bacteraemia or, once bacteraemia is present, the general administration of antibiotic is associated with exposing the inner surface of the catheter, after its closure, at a very high concentration of the adequate antibiotic meant to eradicate the colonisation. This technique proved effective in the case of Gram-negative bacilli and coagulase-negative staphylococci, but it is not recommended in colonisations with *S. aureus* [18].

2.3. Urinary tract infections

UTIs are the most frequent HCAIs. In most hospitals, catheter-related bacteriuria represents 40% of all HCAI within 1 year. The decision to treat is made after discriminating between the presence of bacteria (colonisation) and symptomatic infectious processes. The signs of

Risk factors	Risk distribution
Type of catheter	Polyvinylchloride > teflon > polyurethane, metallic
Catheter site	Central > peripheral
	Femoral > jugular > subclavian
	Lower limbs > upper limbs
Type of placement	By incision > percutaneous
Duration of placement	over 72h > under 72h
Manner of placement	In emergency > selective
Experience of medical staff	Unexperienced staff > specially trained teams

Table 2. Distribution of the infection risk in the intra-vascular catheterisation.

catheter-associated UTIs are fever, lateral lumbar pain, sensitivity in the costovertebral angle, haematuria and delirium with recent onset. After catheter removal, pollakiuria or dysuria may be present.

The Infectious Disease Society of America defines asymptomatic bacteriuria as the absence of symptoms with the presence of over 10^5 colony forming units/ml of one or more bacterial species in a catheterised patient. In most cases of asymptomatic bacteriuria, the treatment led to the temporary sterilisation of urine and not to the eradication of pathogens [19]. Additionally, in 33–50% of patients, after catheter removal, the bacteriuria spontaneously resolved. This is why treating an asymptomatic bacteriuria increases the risk of antimicrobial resistance or of adverse reactions associated with useless antibiotic treatment.

Some pathogenic bacteria produce biofilms, which consist of an adherent layer of microorganisms and their extracellular products. The biofilm protects the pathogens against the host's defence mechanisms and against antibiotic therapy. Migration to the urinary bladder occurs in 1–3 days. The duration of catheterization is an important risk factor, with almost all patients who are catheterised for more than 30 days developing bacteriuria. These patients are at risk of upper urinary tract inflammation, which increases the risk of bacteraemia. Infections linked to long-term catheterisation are often polymicrobial, which involves a broad-spectrum treatment.

The selection of antibiotics used for the treatment of catheter-associated UTIs depends on the result of the microscopical examination, as well as on the colonial characters. In 60–80% of cases, the causative agent is a Gram-negative bacillus (*E.coli*, *Klebsiella* spp., *Pseudomonas* spp., *Proteus* spp., *Enterobacter* spp.). The remaining 20–40% is caused by Gram-positive bacteria, most often species of staphylococci or enterococci. The empirical treatment has to take the following factors, which increase the risk of antibiotic resistance: the duration of hospitalisation, previous administration of antibiotics, and local resistance patterns.

Urinary fluoroquinolones (ciprofloxacin and levofloxacin) are administered to patients with mild and moderate infections, who are considered haemodynamically stable and do not present an altered mental status. Moxifloxacin is not recommended, as it does not reach effective urine concentrations. Broad-spectrum cephalosporins, ceftriaxone or cefepime, may also be used. In patients with urosepsis or in those haemodynamically unstable (hypothermia, tachycardia over 90/minute, tachypnoea over 20 respirations/minute or Pco_2 under 33 mmHg, leukocytosis over 12,000/mm^3 or leukopenia under 4000/mm^3) piperacillin-tazobactam is administered.

In medium clinical forms, ciprofloxacin, 400 mg iv, for every 12 h or levofloxacin 500 mg iv /24 h or ceftriaxone for 1 g iv/day are administered.

The recommended treatments in severe forms include: cefepime 2 g iv/12 h, ceftazidime 2 g iv/8 h, imipenem 500 mg iv/6 h, doripenem 500 mg iv/8 h, meropenem 1 g/8 h and piperacillin/tazobactam 3.375 g iv/6 h.

The treatment of UTIs associated with bladder catheterisation is done with antibiotics for 3 days in women aged over 65 years, from whom the catheter has been removed; otherwise, the treatment is given for 7 days. The duration of levofloxacin treatment is 5 days.

Most hospital-acquired UTIS are expensive and may be prevented. The implementation of protocols based on present guidelines will reduce the inadequate use, as well as the antimicrobial resistance. When catheterisation is necessary, its duration should be limited. In case infections occur, the empirical treatment should be conducted according to the suspected pathogens and on the hospital's antibiogram. When the results of cultures become available, antibiotics narrow their spectrum. The treatment should be limited to 7–14 days, depending on the response to treatment. Catheter removal is a key factor because catheterisation increases the risk for hospital-acquired UTI and other complications, resulting in prolonged hospitalisation and increased costs [20, 21].

2.4. Intra-abdominal infections

Intra-abdominal infections include a series of diseases with variable severity, from uncomplicated appendicitis to faecal peritonitis. Uncomplicated infections involve a single organ and may not reach the peritoneum, and they may be solved either by surgical resection or by administration of antibiotics. Complicated intra-abdominal infections are those which extend to the peritoneum causing localised or generalised peritonitis; in order to solve these, the infection source must be solved by both surgery and antibiotic therapy.

The antimicrobial therapy of intra-abdominal infections, which are to be solved percutaneously or by surgery, has the following goals: to accelerate the elimination of the infecting microorganisms, to decrease the recurrence risk of the intra-abdominal infection, to shorten the clinical evolution, to limit the expansion of the infection to the abdominal wall and to decrease the risk of generalisation of the infectious process.

The antibiotic therapy is initiated after hydroelectrolyte rebalance, the restored volemia determining the restoration of the visceral perfusion and a better distribution of the medication. Moreover, this diminishes the side effects of antibiotics, which have been exacerbated by the deficitary perfusion of internal organs.

The empirical antibiotic treatment is initiated in concordance with the most probable microbiological spectrum, the type and density of germs being dependant on the level where the perforation of the digestive tract has occurred. By gastric, duodenal and proximal jejunal perforations, a low number of aerobic Gram-positive and anaerobic Gram-negative bacteria, generally sensitive to cephalosporins, are released into the peritoneum. *Candida albicans* has also been isolated, but antifungal treatment is only required in the case of patients under immunosuppressive treatment or in patients with recurrent intra-abdominal infections. The perforations of the distal small intestine often evolve as localised abscesses and peritonitis only takes place when these are ruptured. The intra-abdominal infections propagated from the colon into the peritoneum are caused by anaerobic or facultative anaerobic Gram-negative bacteria; *Bacteroides fragilis* is sometimes present.

The selection of the antibiotic should then be guided by the results of the cultures from the biological specimens obtained by percutaneous drainage or during the surgical intervention, but until these become available, it is necessary and useful to perform the microscopical examination directly on a Gram-stained smear. If high numbers of Gram-positive cocci are

present, these are very likely to be enterococci or other faecal streptococci, which imposes the association of vancomycin.

Aerobic and anaerobic Gram-negative cocci may be covered by administration of cefoxitin, ampicillin/sulbactam, piperacillin/tazobactam, imipenem, meropenem, moxifloxacin, while aerobic Gram-negative bacilli may be destroyed with aminoglycosides, second-, third- and fourth-generation cephalosporins, aztreonam, antipseudomonal penicillins or fluoroquinolones (ciprofloxacin, levofloxacin). It must be mentioned that ertapenem is not active on *Pseudomonas aeruginosa* and *Acinetobacter* spp., and in the case of critical patients infected with *P. aeruginosa*, the dose of meropenem must be increased to 1 g administered for every 6 h. Vancomycin-resistant enterococci produce extremely difficult to treat infections, the only useful antibiotic being daptomycin. Tigecycline has been approved for the treatment of complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, E. coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (*vancomycin-susceptible), MSSA, MRSA and some anaerobic bacteria [22].

The antibiotic, which is active only against Gram-negative bacilli and anaerobic bacteria, is metronidazole, for which no resistance has been reported.

The patients at high risk of unfavourable evolution and reserved prognosis have a high APACHE II score, poor nutritional status, significant cardiovascular diseases, immune suppression induced by medicines or by co-morbidities, while the infection source cannot be controlled. The predictive factors of therapeutic failure include the duration of the evolution prior to hospital admission, more than 2 days of presurgical treatment, as well as the presence of the MDRO. These patients should be treated similarly to those with hospital-acquired infections with carbapenems and vancomycin, but also considering the local antibiotic resistance.

The antibiotic treatment must be administered until the resolution of the clinical signs of infection (normalisation of the thermal curve, restoration of the intestinal transit) and normalisation of the biological inflammatory syndrome.

In cases with recurrent intra-abdominal infections, the diagnosis must be reassessed after 5–7 days of treatment and the investigations should be broadened (echography, CT). Often, the antibiotic therapy must be adjusted or a new surgical intervention is required in order to eliminate the site of infection.

2.5. Meningitis

The antibiotic treatment must be urgently initiated, immediately after blood collection for blood culture and after performing the lumbar puncture. Delayed administration of the first dose of antibiotic is associated with an aggravated prognosis, and it is a strong independent factor of increased mortality, exceeding the importance of disease severity upon hospital admission and of the isolation of a penicillin-resistant strain.

The most frequent cause of delayed antibiotic therapy is the missed diagnosis due to an atypical form of meningitis (absence of fever, headache or neck stiffness). Another possible cause of temporization is represented by scheduling the imagistic investigation immediately after admitting the patient in whom the spinal tap is not safe: risk of a cerebral hernia after

cerebrospinal fluid (CSF) collection, in cases of expansive intra-cranial processes accompanied by papilledema or focal signs. In this latter situation, computerised tomography (CT) or nuclear magnetic resonance (NMR) examinations should be conducted after blood collection for blood culture and after the first dose of antibiotic, despite the risk of excessive treatment.

The antibiotic administration route in meningitis is intravenous, which is capable to ensure the CSF bactericidal concentrations; the exception is for rifampicin, which may be administered orally and is useful in the treatment of meningitis caused by beta-lactam-resistant pneumococcus and coagulase-negative staphylococci.

Antibiotic selection: in the treatment of bacterial meningitis, bactericidal antibiotics able to cross the blood-brain barrier are administered, so that optimal CSF concentrations are ensured regardless of the meningeal inflammation degree (meningeal inflammation favours the penetration of the antibiotic in the sub-arachnoid space at the onset of the disease, but as the inflammation regresses under treatment, the concentration tends to decrease, so that higher doses are required as compared to other diseases) [23].

Patients with suspected bacterial meningitis will be initially treated with a broad-spectrum antibiotic concordant to the most probable aetiology, the selection being made depending on the age and comorbidities. After establishing the aetiology and antibiotic susceptibility of the isolated pathogen, the antibiotic therapy will be focused, maintaining the high doses and intravenous administration.

The lumbar puncture should be repeated after the first 24–36 h from the initiation of the treatment in order to assess CSF cytological, biochemical and bacteriological changes.

The immune competent adult with bacterial meningitis requires an initial antibiotic treatment aiming at meningococcus and pneumococcus, consisting in the association of ceftriaxone (2 g/12 h) or cefotaxime (2 g/6 h) with vancomycin (30–60 mg/kg/day for every 8 or 12 h); third-generation cephalosporins must be administered even if the antibiogram shows that the respective strain presents intermediate sensitivity or resistance, because vancomycin acts synergically and increases the efficiency of the therapy [24].

Patients with bacterial meningitis and compromised cell immunity due to pre-existing conditions or immunosuppressive treatment, but with conserved renal function, should be treated with vancomycin (60 mg/kg/day divided into two or three doses) plus cefepime (6 g/day divided into three doses) or meropenem (6 g/day divided into three doses).

If a *Listeria* infection is suspected, the empirical treatment may consist in the association between vancomycin and moxifloxacin (400 mg in a single daily dose) plus trimethoprim-sulfamethoxazole (10–20 mg/kg/day divided at 6 or 12 h).

The duration of the antibiotic treatment in meningitis is not standardised, but it should be individualised based upon the clinical response of each patient, but usually 7 days of treatment is sufficient for meningococcal and *H. influenzae* meningitis, 10–14 days for pneumococcal meningitis, 14–21 days for meningitis with *S. agalactiae* and 21 days or more for meningitis with *L. monocytogenes*; meningitis with aerobic Gram-negative bacilli requires antibiotic administration for 21 or 14 days after the last CSF sterile culture.

Hospital-acquired bacterial meningitis (HABM) may be the result of an invasive procedure (craniotomy, insertion of internal or external ventricular catheter, lumbar puncture, intrathecal medication, spinal anaesthesia), of a complicated cranial trauma or, in more rare cases, of an infectious metastasis in patients with hospital-acquired bacteraemia. Such meningitis is caused by microorganisms with different spectra from community-acquired cases, and the disease is the result of particular pathogenetic mechanisms.

Bacterial meningitis is a redoubtable complication of craniotomy, occurring in 0.8–1.5% of the patients who undergo this procedure. One-third of the post-craniotomy meningitis cases develop during the first week after the surgical intervention, another third during the second week and one-third after the second week from the intervention, sometimes even years after the surgical procedure. The risk of post-surgical meningitis may be minimised by the attentive use of surgical techniques, especially those which decrease the possibility of liquid fistulae. Other factors associated with meningitis after craniotomy include concomitant infection at the incision site and duration of procedure exceeding 4 h.

The incidence of meningitis associated with internal ventricular catheters (cerebrospinal shunt) used in the treatment of hydrocephaly varies between 4 and 17%. The most important causative factor is the colonisation of the catheter at the time of insertion so that most infections become manifest in less than 1 month from the procedure.

External ventricular catheters are used to monitor intra-cranial pressure or to temporarily deviate the CSF if there is an obstruction in the system or as a treatment component in cases of infection of the internal catheter. The rate of external catheter-associated infection is around 8%.

The incidence of meningitis after moderate or severe cranial trauma is 1.4%. The open cranial trauma is encountered in 5% of cranial trauma and is complicated by meningitis in 2–11% of cases. Most patients in whom meningitis occurs as a complication of closed cranial trauma present a skull base fracture, which creates a communication between the sub-arachnoid space and the sinus cavities, posing an infection risk of up to 25%. The average time interval between the trauma and the onset of meningitis is 11 days. The CSF leak is the major risk factor, even though most post-traumatic leaks are not diagnosed. Most fistulae resolve spontaneously within 7 days, a surgical intervention is recommended if the breach persists. The cranial trauma is the most frequent cause of recurrent meningitis.

The diagnostic procedure relies on neuroimagistic investigations, CSF analysis (cell count, biochemical tests for glucose, proteins, Gram staining, cultures) and blood cultures. Neuroimagistics is indicated in most patients as it allows the ventricular size evaluation and brings information on a possible poor functioning of the shunt or the presence of residual catheters after previous surgical interventions.

The most frequently encountered bacteria in these cases are Gram-negative bacilli (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), *S. aureus* and coagulase-negative staphylococci.

The empirical antibiotic therapy in HABM depends on the pathogenesis of the infectious process. In patients with meningitis occurring after neurosurgical interventions, or in patients with long-term hospitalisation after open cranial trauma or skull base fractures, vancomycin is associated with cefepime, ceftazidime or meropenem; the second antibiotic is selected

depending on the local chemotherapeutics susceptibility profiles of Gram-negative bacilli. The empirical treatment in skull base fracture or early after ENT surgery includes vancomycin plus a third-generation cephalosporin (cefotaxime, ceftriaxone). After isolating the involved pathogen, antimicrobial therapy is changed for an optimal management. Linezolid and daptomycin are effective in staphylococcal meningitis; linezolid has good pharmacokinetic properties—CSF penetration is around 80%.

The initiation of empirical treatment is recommended in all patients with post-surgical signs of meningitis; this is withdrawn after 72 h in case the results of CSF cultures are negative. The treatment must be individualised, especially in patients previously treated with antibiotics, in whom the treatment is continued despite the negative results of cultures.

Given the emergence of MDR Gram-negative bacilli, the antimicrobial therapy of HABM caused by these pathogens becomes problematic. This is especially true in cases of HABM caused by *Acinetobacter baumannii* species, bacteria with acquired resistance to third- and fourth-generation cephalosporins and even to carbapenems. The treatment of *Acinetobacter* meningitis includes meropenem associated with an aminoglycoside administered intra-ventricularly or intrathecally. If the identified isolate is resistant to carbapenems, intra-ventricular or intrathecal administration of colistin or polymyxin B will be given instead of meropenem.

Treatment protocols recommended depending on the pathogenesis of the infectious process:

- *Infection after neurosurgical procedure*—Gram-negative bacilli (including *P. aeruginosa*), *Staphylococcus aureus* and coagulase-negative staphylococci (*S. epidermidis*) may be involved. Vancomycin plus cefepime or meropenem are recommended.

- *Ventricular or lumbar catheter*—coagulase-negative staphylococci, *S. aureus*, Gram-negative bacilli (*P. aeruginosa*) and *Propionibacterium acnes* may be present. Vancomycin plus cefepime or meropenem are recommended.

- *Penetrating trauma: S. aureus*, coagulase-negative staphylococci, Gram-negative bacilli. Vancomycin plus cefepime or meropenem is administered.

- *Skull base fracture: Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*. Vancomycin plus a third-generation cephalosporin (ceftriaxone or cefotaxime) is recommended.

2.6. Infections of the skin and soft tissues

With the increasing incidence of MRSA, skin and soft tissue infections require more frequent admission of patients presenting tissue necrosis, fever, hypotension, intense pain, altered consciousness, respiratory, hepatic or renal failure, to the ICU. When choosing the therapeutic scheme, the possibility of a polymicrobial infection must be considered, with consecutive need to cover not only MRSA but also Gram-negative and anaerobic bacteria. An inadequate initial empirical treatment is associated with prolonged evolution and hospital stay [25].

Perianal infections and abscesses, infected decubitus ulcers, and moderate and severe infections of the diabetic foot frequently involve multiple aetiologies and require coverage for

streptococci, MRSA, aerobic and anaerobic Gram-negative bacilli until the results of micro-biological investigations become available.

In the case of patients with non-suppurative cellulitis, a beta-lactam antibiotic, such as cefazo-lin, may be initially prescribed, which is to be replaced in case of unsatisfactory clinical evolu-tion. The replacement will be made according to the result of the antimicrobial susceptibility test or with an antibiotic active on MRSA, if the pathogen has not been isolated in the culture. The empirical treatment of MRSA infections may include vancomycin, linezolid, daptomycin, tigecycline and telavancin. Linezolid, daptomycin, vancomycin and telavancin additionally also cover streptococcal infections and not only MRSA.

In case of a documented or suspected staphylococcal infection, the recommendation is to immediately initiate the antibiotic treatment according to maximal probability criteria and according to local data on the sensitivity of strains circulating in the respective area. The doses of antibiotic must be adequate, because sub-inhibitory concentrations favour the release of staphylococcal toxins and virulence factors (PVL—Panton-Valentine leukocidin), which trig-ger the onset of skin, lung or bone necrotic lesions. Catheters and intra-vascular devices must be removed. In cases with detected abscesses, these should be drained; the localised infection of a prosthetic joint requires the removal of the prosthesis, but if the infection is located on a valvular prosthesis, its removal is not always required.

The treatment of MRSA infections frequently includes the administration of vancomycin. The increased vancomycin consumption has posed an increasing selection pressure of staphylo-coccal strains resistant to this antibiotic. The concentration of vancomycin required to inhibit most *S. aureus* strains is 0.5–2 mg/l. The strains with a minimum inhibitory concentration (MIC) of vancomycin between 8 and 16 mg/l are classified as intermediate sensitive or VISA (vancomycin-intermediate *S. aureus*), while strains with MIC ≥32 mg/l are considered resis-tant or vancomycin-resistant *S. aureus* (VRSA). The resistance mechanisms are different in the two types of strains: in VISA strains, the bacterial cell wall is thickened by the altered biosynthesis process and the glycopeptides targets are hidden in its thickness and in the case of VRSA strains, the target of glycopeptides is itself modified.

Surgical wound infections are another category of infections frequently confronting ICUs. In their most frequently polymicrobial aetiology, Gram-positive cocci (especially MRSA), *Enterobacteriaceae* and non-fermentative Gram-negative bacilli (*P. aeruginosa*) are among the most frequently isolated pathogens. The empirical treatment of these infections consists of associating cefepime or meropenem with an aminoglycoside or a fluoroquinolone.

Many extrinsic risk factors are inter-connected with intrinsic factors or are found in asso-ciation, for which reason, the Study on the Efficacy of Nosocomial Infections Control (SENIC), a risk index, has been proposed for surgical wound infections. When compared to the traditional Altemeier system, this index predicts the risk of post-surgical infection two times better and the inclusion of other items does not seem to improve its predic-tive capacity [26]. The National Surveillance System of Nosocomial Infections in the USA proposed the NNIS risk index, further completed with the item on the use of laparoscopic techniques (**Tables 3** and **4**).

SENIC index			NNIS index	
Item	**Score**		**Item**	
1. Operating time > 2 ore	1 point		1. Class ASA 3/ 4/ 5	1 point
2. Abdominal surgery	1 point		2. Contaminated or septic surgery	1 point
3. Contaminated or septic surgery	1 point		3. Duration of surgical procedure > T (variable time depending on the operating procedure)	1 point
4. Presence of at least 3 diagnosis	1 point		4. Use of laparoscopic technique	-1 point
SENIC score = Σ item 1,2,3,4			NNIS score = Σ item 1,2,3,4	

Table 3. Risk indexes for post-surgical wound infections.

Class	Classification	Infection rate	
		With presurgical antibiotic prophylaxis	**Without presurgical antibiotic prophylaxis**
Class I	Clean surgery	5.1%	0.8%
Class II	Clean-contaminated surgery	10.1%	1.3%
Class III	Contaminated surgery	21.9%	10.2%
Class IV	Septic surgery		

Table 4. Risk of post-surgical wound infection depending on the Altemeier classification.

3. Management of antibacterial chemotherapeutic drugs

The choice of antibiotics is conditioned by:

- the characteristics of the isolated or suspected aetiological agent,

- patient characteristics, which may influence the efficiency and toxicity of the treatment (age, physiological status, comorbidities, infection site),

- pharmacodynamic and pharmacokinetic characteristics of the antibiotic (adsorption, tissue distribution, concentration in the infectious focus, metabolisation and elimination of the antibiotic).

In the case of the critical patients, the early administration of an effective antibiotic treatment is essential and determining, the time until the initiation of therapy being a strong predictor of mortality. A retrospective cohort study showed that the delay of effective treatment after the onset of recurrent or persistent hypotension was associated with an increased death risk; the survival rate in patients with treatment administered during the first hour was of 79.9%, with each hour of delay in antibiotic therapy leading to a 7.6% decrease in this rate [27].

Optimization of doses. The antibiotic requirement is calculated depending on the characteristics of the patient (age, weight, renal function), on the pathogenic microorganism, infection site

(endocarditis, pneumonia, meningitis, osteomyelitis) and the pharmacokinetic and pharmacodynamic characteristics of the drug [28].

The loading dose is probably the most important and depends on the distribution volume of the drug and on the intended plasmatic concentration, regardless of the renal function. Antibiotics are classified according to multiple criteria, one being the criterion, which influences the dosage: the doses of hydrophilic antibiotics (beta-lactam) must be increased during the first stages of sepsis, together with the increase in the extravascular space. The doses of lipophilic antibiotics are influenced by other factors, such as obesity [7, 28].

Before establishing the rational antibiotics administration regimen, the antimicrobial activity in time must be understood, i.e., the pharmacodynamics of the drug in question (the relationship between its serum concentration and its therapeutic effect). From a pharmacodynamic perspective, antimicrobial agents may be divided into:

- The bactericidal effect of beta-lactam antibiotics is independent of their concentration, as long as this exceeds the MIC and they do not possess a significant post-antibiotic effect (PAE) (The inhibition of bacterial growth continued for a variable period after the concentration of antibiotic at the infection site has dropped under the MIC.) The strategy to obtain optimal results is to increase the exposure time of microbes to plasmatic concentrations of antibiotic exceeding the MIC, which is accomplished by frequent doses, by the administration at short time intervals or by continuous infusion.

- The bactericidal effect of vancomycin, carbapenems, macrolides, clindamycin, azoles, linezolid is independent of their concentration, if this is higher than the MIC, but it is time dependent. The PAE is intermediate (The serum antibiotic levels may drop under the MIC for a short while.) The antibiotics in this group produce optimal results when administered in lower but with more frequent doses.

- The bactericidal effect of aminoglycosides, fluoroquinolones and metronidazole is dose dependent and has a significant post-antibiotic effect (Bacterial growth is prevented even if tissue levels decrease under the MIC for longer periods of time.) This is why higher doses, but at larger intervals, may be administered, with 2–4 h between the doses after being admitted, during which time the plasmatic concentration of these antibiotics may be undetectable, which reduces their nephrotoxicity.

The time-dependent bactericidal effect is achieved by optimising the duration of bacterial exposure to antibiotics, while the dose-dependent bactericidal effect is maximal when the antibiotic concentration is maximal [7].

Polymyxins are concentration-dependent antibiotics; they are active on carbapenemase-producing bacteria, and they are increasingly kept as last therapeutic option in infections with resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. We must underline the fact that if sub-optimal doses of colistin are administered, the pathogen gains resistance.

First-line antibiotic treatment in severe acute infections.

Severe acute infections are classified as community-acquired, healthcare-associated and hospital-acquired infections. For the practical assessment of a case, Yehuda Carmeli proposed a score, which allows the stratification of risk factors for the infections with resistant or MDRO, depending on the previous contact of the patient with the health care sector, on the existence in his/her medical history of antibiotic treatments, as well as on associated factors (immune suppression, co-morbidities):

Risk assessment for infections with resistant or MDR pathogens:

a. Contact with the health care sector:

  1. No contact—1

  2. Contact without invasive procedures—2

  3. Repeated contacts with invasive procedures—3

b. Previous antibiotic treatment:

  1. No antibiotics—1

  2. With antibiotics—2

c. Characteristics of the patient:

  1. Young, without co-morbidities—1

  2. Elderly, with co-morbidities—2

  3. Immunocompromised patient (AIDS, neoplastic diseases)—3

According to this score, the value 1 corresponds to community-acquired infections, the value 2 corresponds to HCAI and the value 3 to hospital-acquired infections. The Carmeli score may only be 1, 2 or 3, and it is given by the highest value obtained from the answers to the three categories of questions [29]. This classification allows a correlation between the type of infection, the most probable aetiology and the estimation of the antibiotic susceptibility of the microorganism in question.

The empirical or first-line treatment is especially important for the evolution of the infection; the delayed initiation of an effective antimicrobial treatment leads to increased morbidity and mortality, aggravated and generalised infections, as well as increased health care costs. If the initial treatment has not been effective, adding a new antibiotic or replacing the initial one with a broader spectrum antibiotic (escalation) will not increase the chance of favourable evolution. The adjustment of antibiotic treatment after the microbiological results become available might be tardy and ineffective, if the initial treatment has been inadequate, especially in the case of hospital-acquired infections (multivariate analysis have demonstrated that inadequate empirical treatment increased the risk of mortality). The association of antibiotics of different classes is useful in the initial treatment of infections with MDRO.
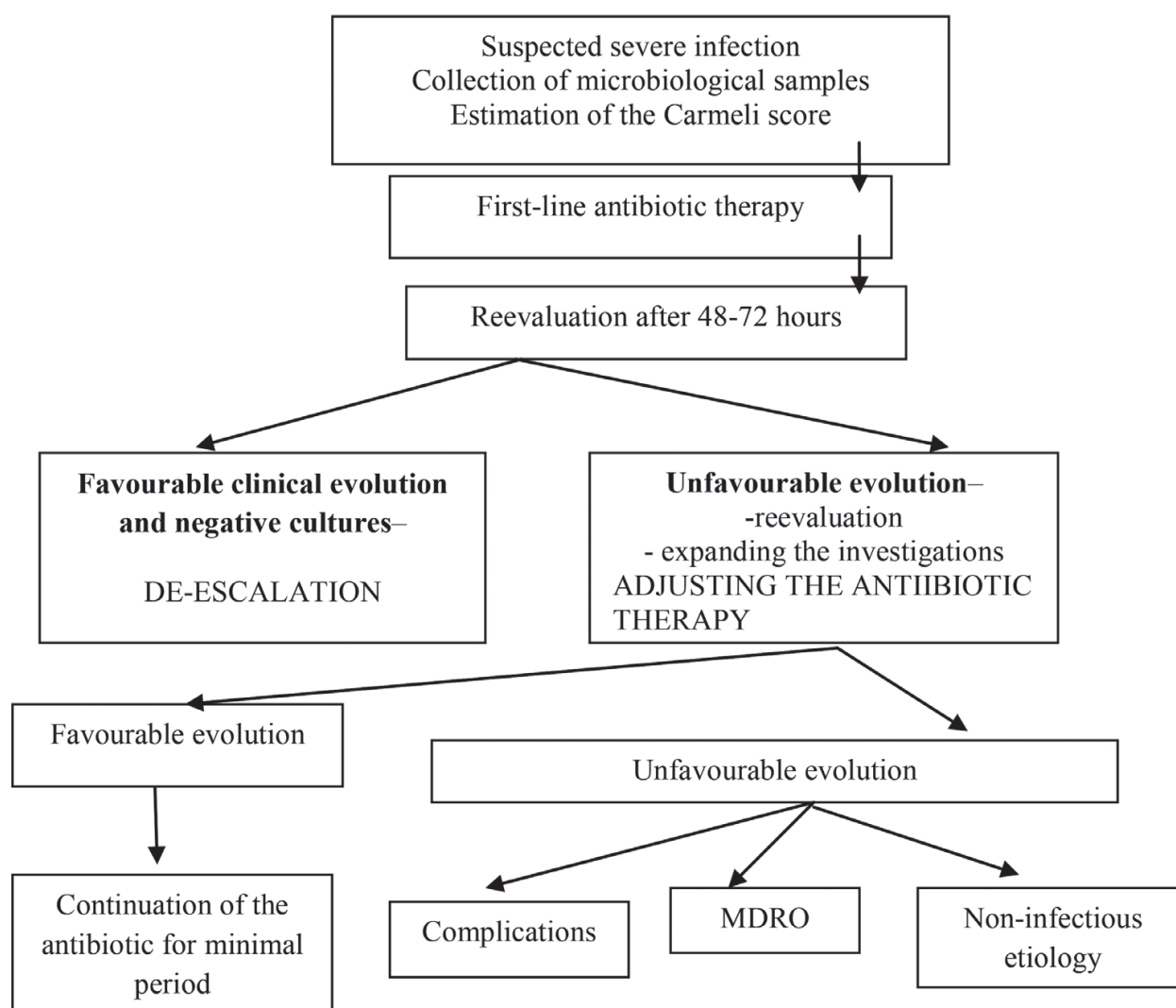
Figure 2. Algorithm for initiation of antibiotic therapy.

In patients with severe infections, the recommendation is to administer the antibiotic treatment during the first hour after the diagnosis, but not before collection of blood and other biological samples required for the identification of the aetiological agent and testing for its sensitivity to chemotherapeutics. Patients with meningitis will receive antibiotic treatment during the first 30 min after hospital admission, immediately after collection of blood and CSF [1, 10].

The empirical or first-line antibiotic treatment is initiated according to the most probable microbiological spectrum and consists of the administration of a broad-spectrum antibiotic (covering Gram-positive cocci, including MRSA and enterococci, as well as Gram-negative bacilli, including *Acinetobacter* spp., *Pseudomonas aeruginosa* and *Enterobacter* spp.) for a short period of time, i.e., for 2–3 days. Depending on the clinical evolution of the patient and on the results of microbiological tests, the initial treatment scheme may be modified by decreasing the number of antibiotics or reducing the spectrum (*de-escalation*). Narrowing the therapeutic regimen does not only refer to the shift from a broad-spectrum to a narrow-spectrum antibiotic, but also to adjusting (reducing) the doses and treatment duration [30].

The Principles of de-escalation are as follows:

- administration of an ultra-broad-spectrum antibiotic for a short period of time,

- identification of the aetiology within this covered period,

- replacement of the initial antibiotic with a narrow-spectrum antibiotic.

If, after 48–72 h of treatment with a broad-spectrum antibiotic, the status of the patient does not improve, the available microbiological data are attentively reanalysed and the possibility of MDRO infection, a non-bacterial or even a non-infectious aetiology, are considered. The evaluation must also include the possibility of a complication, such as the formation of an abscess, empyema, etc. [31].

Decreasing the risk of adverse reactions, the decreased selection pressure of resistant strains, as well as the reduction of costs represent the benefits of de-escalation and treatment cessation after a shorter time. Examples of benefits in the administration of antibiotics in short cures and/or reduction of the antibiotics spectrum include the decrease in the incidence of cases of diarrhoea with *Clostridium difficile* and of infections with resistant bacteria and *Candida* spp. (**Figure 2**).

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