Strategies for empiric antibiotic therapy in severe sepsis

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Abstract

Severe sepsis and septic shock remain the leading causes of multiple organ failure and mortality in surgical intensive care units. Early antibiotic therapy recently became a challenge, because of the increased number of infections caused by multiple drug resistant bacteria, with Gram-negative bacteria such as Klebsiella pneumoniae and Pseudomonas aeruginosa being the most frequently cultured pathogens.

In this review, detailed recommendations for the treatment of various infections are presented and discussed, with particular emphasis on the determination of empiric antibiotic therapy in the early stages of sepsis and localised infections.

Key words: antibiotics, empiric therapy, sepsis

Despite the long-term studies and recommendations formulated by the Surviving Sepsis Campaign (SSC), severe sepsis causes of extremely high mortality reaching 29–75% [1, 2, 3]. In the studies involving surgical ICU patients, the mortality associated with intra-abdominal infections ranged from 22% to 72% [1, 4]. The alarmingly increased numbers of patients with severe sepsis have been observed during the postoperative period. The analysis of data of 2039776 surgical patients revealed that the incidence of severe sepsis increased from 0.3% in 1997 to 0.9% in 2007 compared to the total population of admitted patients [5]. The study conducted by the Polish Working Group for Sepsis demonstrated that surgical patients constituted the largest group of ITU patients treated due to sepsis whose primary sources were intra-abdominal infections (47%), followed by respiratory (28%), blood (10%) and urinary (4%) infections [6]. The multi-centre analysis of 3147 individuals carried out by the European Sepsis Occurrence in Acutely Ill Patients (SOAP) showed that respiratory infections were responsible for sepsis in 49% of patients whereas intra-abdominal infections for 21% of cases [1]. Antibiotic therapy is one of the essential elements of severe sepsis management, which definitely affects survival rates [7].

The increasing antibiotic resistance of bacterial strains has been observed worldwide; therefore, the resistance-related were taken into account in numerous recommendations for empiric antibiotic therapy. In 2004, the Infectious Diseases Society of America (IDSA) listed 6 bacterial species, i.e. Enterococcus spp., Methicillin-Resistant Staphylococcus Aureus (MRSA), Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa, Acinetobacter baumannii and called them the alarm pathogens [8]. Recently, this group of bacteria was widened with Clostridium difficile, due to its increasingly high resistance to metronidazole [9].

Multi-resistance, observed mainly in the hospital setting, affects also the personnel members and their families. In the case of Pseudomonas aeruginosa, the risk factors of multi-resistant strain infections include long hospital stay, ITU treatment, earlier antibiotic therapy, artificial lung ventilation, neoplastic diseases, chronic obstructive pulmonary disease, and past infections caused by this microorganism [10]. The emergence of extensively drug-resistant (XDR), multidrug-resistant (MDR) and pandrug-resistant (PDR) bacterial strains reduces the efficacy of treatment, irrespective of the differences in resistance definitions presented in literature [8, 11]. In clinical practice, the production of Gram-negative extended-spectrum beta-lactamases (ESBLs+), AmpC, and metallo-beta-lactamases (MBLs) is of significance. MBLs break down carbapenems. The most dangerous mechanisms of resistance characterise Klebsiella pneumoniae (and other Gram-negative bacilli) producing Klebsiella Pneumoniae carbapenemases (KPCs), which hydrolyse carbapenems and the remaining beta-lactam antibiotics [12, 13]. The KPC+ strains are usually susceptible only to colistin, tigecycline, gentamicin, occasionally to amikacin [12]. The presence of ESBL+ amongst Gram-negative bacilli
leads to the lack of resistance to penicillins, cephalosporins, and monobactams [14]. These bacteria are likely to be susceptible only to carbapenems (imipenem, meropenem, doripenem), also when combined with aminoglycosides or fluoroquinolones.

According to the current guidelines, the empiric therapy when ESBL(+) are present should not include penicillins and cephalosporins combined with beta-lactamase inhibitors, expect for urinary infections in which their use is acceptable. The presence of this type of beta-lactamases is likely to cause simultaneous resistance to fluoroquinolones, co-trimoxazole, tetracyclines, and aminoglycosides [14]. The key drugs for the treatment of Pseudomonas spp. infections are piperacillin with tazobactam, ticarcillin with clavulanic acid, ceftazidimes, cephapim, aztreonam, aminoglycosides, ciprofloxacin and levofloxacin. To the widespread resistance, the clinical usefulness of some of the above-mentioned antibiotics and chemotherapeutics appears doubtful; therefore, they should be used only when the local resistance has been known. The MDR Pseudomonas aeruginosa bacteria of acquired different mechanisms of resistance, e.g. by synthesis of Verona integron-encoded (VIM) and imipenemase (IMP) MBLs and ESBLs(+), can be susceptible only to colistin.

The findings of the European Antimicrobial Resistance Surveillance (EARS) carried out in 2009 demonstrated that in Poland the percentage of Pseudomonas aeruginosa strains resistant to carbapenems was 25%, to piperacillin 30%, to fluoroquinolones 36%, to ceftazidime 21%, and to aminoglycosides 27% [15].

Multi-resistant Acinetobacter baumannii are likely to be susceptible only to carbapenems, colistin, less commonly to tigecycline, sulbactam (not approved in Poland), aminoglycosides, or tetracyclines. However, there were some cases of resistance to carbapenems, e.g. when the strain produced oxacillinase (OXA) [16, 17]. Based on the Polish hospital data, Acinetobacter baumannii strains showed the highest susceptibility to carbapenems, netilmicin and ampicillin with sulbactam [18]. In bacteremia caused by MDR Acinetobacter baumannii the combined treatment with carbapenem and ampicillin together with sulbactam showed higher clinical efficacy compared to carbapenem combined with ampicillin or carbapenem monotherapy [19]. Moreover, the successful clinical treatment of MDR Acinetobacter baumannii infection using simultaneously meropenem, colistin and tigecycline was reported [20].

Recently, a new subgroup of MBLs, designated New Delhi MBL (NDM-1) was detected amongst Klebsiella pneumoniae species in India. The bacteria producing NDMs are resistant to many groups of antibiotics, such as fluoroquinolones, aminoglycosides, beta-lactams (including carbapenems), and are susceptible only to colistin and tigecycline [21]. At present carbapenem remains the basic therapeutic option for severe infections in ITU patients [22, 23], although research is being continued to find new therapeutic measures and new drugs [23].

The "last resort" therapy in infections caused by MDR and PDR bacteria is colistin, more so since the data regarding its toxicity were verified [24]. The use of colistin (3 mln IU every 8 h) for sepsis caused by MDR Pseudomonas aeruginosa or Acinetobacter baumannii (strains susceptible only to colistin) in 28 ITU patients resulted in positive clinical responses in 73% of individuals, nevertheless the 30-day mortality in this group was 42.3% [25]. According to another study involved 78 ITU patients treated due to sepsis caused by similar pathogens, the use of colistin was associated with similar clinical effectiveness (76.9%) [26]. Moreover, the efficacy of high doses of ampicillin with sulbactam or colistin in cases of ventilatory-associated pneumonia (VAP) of MDR Acinetobacter baumannii aetiology was compared. The comparison revealed that the incidence of pathogen eradication (66.6% vs. 61.5%), 14-day mortality (15.3% vs. 20%) as well as 28-day mortality (30% vs. 33%) were not significantly different [27]. Another comparison of efficacy of colistin and imipenem for VAP caused by MDR Acinetobacter baumannii demonstrated similar mortality rates (38% vs. 35.7%) [28].

The therapeutic success is markedly dependent on the antibiotic dose. In the study involving 13 ITU patients with VAP treated with colistin at a dose of 2 mln IU every 8 h, serum drug C\text{max} under stationary conditions was 2.21 mg L\textsuperscript{-1} and was undetectable in the alveolar lavage fluid [29]. This dose can be considered insufficient, which is confirmed by the data reported in previous studies [30, 31]. The effectiveness of MDR Acinetobacter baumannii-caused VAP can be improved by combined administration of colistin and rifampicin [32] or rifampicin with imipenem [33]. The findings of 17 clinical trials and analysis of 5057 clinical isolates of Enterobacteriaceae (Escherichia coli and ESBL(+)) Klebsiella pneumoniae from the urinary tract) demonstrated that phosphomycin (whose intravenous preparation is approved in Poland) is active against 96.8% and 81.3% of strains, respectively. Therefore, its use could be considered as further therapy of some infections caused by multi-resistant ESBL(+) producing enterobacteria [34]. In meningococcal sepsis, penicillin can be used but only for targeted treatment after determination of MIC. According to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), MIC ≤ 0.064 mg L\textsuperscript{-1} allowing to use penicillin whereas its value > 0.25 mg L\textsuperscript{-1} evidences the microorganism resistance. For empirical therapy of infections caused by Neisseria meningitides, ceftriaxone or cefotaxime, alternatively with meropenem are recommended. According to EUCAST guidelines, MIC threshold value for Neisseria meningitidis strain susceptible to ceftriaxone and cefotaxime is ≤ 0.125 mg L\textsuperscript{-1}. 

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The EARS showed that in Poland the percentage of *Streptococcus pneumoniae* strains resistant to penicillin was 30% [15]. Penicillin-resistant strains may be susceptible to third and fourth generation cephalosporins, levofoxacin, moxifloxacin, vancomycin and linezolid. In cases of pneumococcal meningitis, ceftriaxone and cefotaxime show the best penetration of CNS (cerebrospinal fluid). High-level resistance of *Staphylococcus pneumoniae* to penicillin (MIC > 2 mg L\(^{-1}\)) according to EUCAST precludes also the use of third-generation cephalosporins for the treatment of meningitis (if MIC for cefotaxime is >0.5 mg L\(^{-1}\)) and necessitates the administration of vancomycin or linezolid therapy.

Amongst the new “respiratory” fluoroquinolones, levofloxacin and moxifloxacin are of the highest clinical significance. The study encompassing 71973 patients demonstrated that *Streptococcus pneumoniae* resistance to levofloxacin was lower than 1% and amongst penicillin-resistant strains — 0.9–2.7%. Moreover, all *Haemophilus influenzae* and *Moraxella catarrhalis* strains studies were found susceptible to levofloxacin [35]. In cases of *Streptococcus pneumoniae* pneumonia, immunomodulatory macrolides should be taken into consideration.

When *Staphylococcus aureus* infection is suspected, the determinations of oxacillin resistance (methicillin-susceptible strain) and MIC for vancomycin become the priority. According to the EUCAST recommendations in force in Poland, *Staphylococcus spp.* shows susceptibility to vancomycin at MIC ≤ 2 mg L\(^{-1}\). In one of the studies regarding ventilator-associated and hospital pneumonia caused by MRSA, vancomycin was used; the findings demonstrated simultaneous increased mortality and MIC values for vancomycin, even when the strain was considered according to Clinical and Laboratory Standards Institute (CLSI) microbiologically susceptible (MIC ≤ 4 mg L\(^{-1}\)) [36].

The number of *Staphylococcus aureus* species resistant to methicillin has been increasing for many years, and the resistance incidence in western Europe has been estimated at 50% whereas in the USA even at 40–60% [37]. In Poland, this incidence is 20% on average [15]. Since the community-associated MRSA (CA-MRSA) and healthcare-associated MRSA (HA-MRSA) have occurred outside the hospital environment (particularly in the USA), many recommendations and empiric antibiotic therapy consider the use of vancomycin. The CA-MRSA strains primarily cause skin and subcutaneous tissue infections as well as pneumonia (in patients after viral infections). These strains are susceptible to vancomycin, linezolid, quinupristin-dalfopristin, daptomycin as well as clindamycin, trimethoprim-sulfamethoxazole and minocycline (not approved in Poland). When MRSA infection is suspected, vancomycin (also combined with rifampicin) or linezolid, teicoplanin, tigecycline, daptomycin, and quinupristin/dalfopristin should be considered [38].

In Poland, the percentages of MRSA strains resistant to tetracyclines (61–75.8%), macrolides (30.2%), lincosamides (30.2%) (with MLS\(_B\) resistance), cotrimoxazol (75.8%) are found to be high [39], which limits their use even for targeted therapy. The analysis of two clinical trials (involving 1019 patients), comparing the efficacy of linezolid and vancomycin in the treatment of HAP and VAP, demonstrated higher clinical efficacy of linezolid (59 vs. 35.5%) and higher percentages of survival (80 vs. 63.5%) [40]. The clinical studies showed high concentration of linezolid in the lung parenchyma and alveolar fluid (17.7 and 14.4 mg L\(^{-1}\), respectively) [41], whereas the serum concentration of vancomycin in the alveolar fluid and pulmonary parenchyma was 5–25% and 25–41%, respectively [42]. In another two studies, linezolid was found to have a higher index of CSF penetration — 0.66 [43] compared to that of vancomycin used in cerebrospinal meningitis, which ranged from 0.29 to 0.48 [44].

In cases of M SSA infections, the following drugs are used: cloxacillin or another penicillin combined with beta-lactamase inhibitor, e.g. amoxicillin/clavulanic acid or ampicillin/sulbactam, first generation cephalosporins (e.g. cefazolin), macrolides, tetracyclines, trimetoprim/sulfamethoxazol, fluoroquinolones (e.g. moxifloxacin).

The atypical pathogens (*Legionella, Chlamydia pneumoniae, Mycoplasma*) are responsible for 15% of pneumonia acquired outside hospital; therefore, the authors of some guidelines recommend combined therapy (beta-lactam antibiotic with macrolide or tetracycline). In the Australian study involving patients with community-acquired pneumonia caused by atypical pathogens, the combined therapy with beta-lactam antibiotic plus doxycycline was associated with quicker clinical stabilisation and shorter hospital stay (from 6 to 3 days) compared to the treatment with beta-lactam antibiotic and macrolide [45].

The use of macrolides is indicated exclusively when atypical pneumonia (*Chlamydia pneumoniae, Legionella pneumoniae, Mycoplasma pneumoniae*) is suspected. It was demonstrated that early (within 24 h) administration of macrolide is associated with 50% shorter hospitalisation as compared with ceftriaxone therapy [46]. The excellent penetration and accumulation of macrolides in the alveolar macrophages should be emphasised. The levels of azithromycin in these cells are 23-fold and of clarithromycin 70-fold higher than those noted in blood serum [47]. According to Polish recommendations, in severe community-acquired pneumonia cases requiring ITU treatment, ceftriaxone or cefotaxime with macrolides is advised for empiric therapy [48]. The ventilator-associated pneumonia or hospital pneumonia cases need different empiric antibiotic therapy, depending on the time of diagnosis (early or late) and risk factors (age, immunosuppression, risk of *Pseudomonas spp.* infection, MRSA infection, aspiration, COPD).
The severe urinary infections (both acquired outside hospital and hospital ones associated with urinary catheters), which are likely to lead to severe sepsis are most commonly caused by *Escherichia coli*. The community-acquired infections in young women are often caused by *Staphylococcus saprophyticus* [49]. With the prolonged use of urinary catheters, the etiological factors of urinary infections can be multi-resistant to Gram-negative and Gram-positive bacteria (*enterococci*, *staphylococci*). In Poland, the lowest resistance of *Escherichia coli* strains was noted to aminoglycosides (7%), third generation cephalosporins (9%) and fluoroquinolones (23%) [15].

The empiric therapy of severe infections originating from the urinary tract is mainly based on beta-lactam antibiotics: third and fourth generation cephalosporins, half-synthetic penicillin with beta-lactamase inhibitor (amoxicillin/clavulanic acid, piperacillin/tazobactam, and ampicillin/sulbactam) combined with aminoglycoside. Alternatively, carbapenems (imipenem, meropenem, ertapenem) and aztreonam are recommended. In the group of quinolones, levofloxacin is most extensively excreted with urine (84%), followed by ciprofloxacin and moxifloxacin — 43 and 20%, respectively [50]. The drugs used for enterococcal infections include ampicillin, ampicillin/sulbactam, ampicillin/clavulanic acid, aminoglycosides (gentamicin), teicoplanin, vancomycin, linezolid and tigecycline. The empiric therapy of such infections should consider possible resistance to high doses of aminoglycosides (HLEAR strains) and vancomycin (VRE strains). The resistance of *Enterococcus faecalis* to aminoglycosides in Poland is < 1%, which is similar to resistance to vancomycin whereas 39% of strains are found to be HLEAR (High Level Aminoglycosides Resistant) strains [15]. Due to high resistance to aminopenicillins (98%) and high doses of aminoglycosides (75%) for empiric treatment of *Enterococcus faecium* infections, the above antibiotics should not be applied [18]. The analysis of susceptibility of bacteria isolated from Lower Silesia patients with severe infections showed high susceptibility of *Enterococcus faecalis* (87,5%) and *Staphylococcus aureus* (93%) to tigecycline [51].

The blood infections associated with central venous catheters are primarily caused by coagulase-negative staphylococci, including MRCNS, MRSA, and Gram-negative multi-resistant hospital bacteria and fungi. Severe sepsis associated with vascular catheters should be treated empirically with broad-spectrum antibiotics: third/fourth generation cephalosporins or carbapenem or beta-lactam with beta-lactamase inhibitor (with possible addition of aminoglycoside) combined with vancomycin or teicoplanin. This management should be continued until the pathogen has been identified (especially at higher risk of methicillin-resistant strains). The de-escalation to cloxacillin (or cefazolin) is recommended once the MSSA infection has been confirmed [52, 53]. The use of anti-fungal agents (preferably echinocandins or fluconazole in selected cases) for empiric treatment is recommended when the risk factors of candidaemia are present.

In cases of catheter-associated blood infection in patients with severe sepsis and neutropaenia, colonized with Gram-negative MDR strains, the antibiotic active against the colonizing microorganisms should be applied. If the prevalence of MRSA strains of high MIC to vancomycin is found to be increasing in the ward, daptomycin is advised [52, 53]. Irrespective of the infection type (local, generalised, especially accompanied by bacteraemia or fungaemia), in cases of catheter-associated infections, catheters should be removed [2, 52, 54, 55].

The likely etiological factors in intra-abdominal infection complicated with sepsis involve *Escherichia coli*, *Enterococcus faecium*, *Enterococcus faecalis*, *Enterobacter spp*, *Pseudomonas aeruginosa*, *Acinetobacter spp*, *Staphylococcus aureus* (including MRSA), anaerobic bacteria and anascogenic yeasts. Broad-spectrum antibiotics (penicillins with beta-lactamase inhibitors or carbapenems) or combination of third- or fourth-generation cephalosporin or quinolone with metronidazole or tigecycline should be used for empirical treatment of intra-abdominal infections.


The fungal infections in critically ill patients are most commonly caused by *Candida albicans*, although *Candida non-albicans* become increasingly dangerous. The empiric therapy of severe fungal sepsis in haemodynamically unstable patients, not immunosuppressed but with risk of *Candida non-albicans* infections is mainly based on echinocandins [54, 55]. The *Aspergillus spp.*, *Mucor*, *Histoplasma* infections, less common fungal infections, occur primarily in immunocompromised patients. The first-line drug in the treatment of *Aspergillus spp.* infection is voriconazole [56].

In patients with haematological diseases, many guidelines recommend empiric antifungal therapy even in cases of high-risk patients, with prolonged neutropaenia and fever despite broad-spectrum antibiotic therapy administered.
ments and advise everyday evaluation of results to optimise for antibiotic treatment regard pharmacokinetic properties sepsis or septic shock) [64–82]. Numerous recommendations international scientific societies may be helpful in empiric is-inducing strain susceptibility and MIC from the direct [62]. Moreover, it is essential to determine quickly the sep- the regional or national epidemiological situation is needed ward. In community-acquired infections, the knowledge of epidemiological and bacteriological conditions in a given treatment of nosocomial infections should be based on the

According to the general rules of antibiotic therapy of severe sepsis and septic shock, the biological material should be collected for bacteriological tests before the in-

The combination antibiotic therapy (lasting shorter than 3–5 days with subsequent de-escalations depending on the susceptibility of cultured microorganisms) should be used only in cases of Pseudomonas aeruginosa infections and patients with neutropaenia [2]. The guidelines of the Consensus Conference of the Polish Group for Sepsis recommend the use of antibiotics preferably within the first 30 min after diagnosis, and obligatorily during the first hour. The empiric administration of several antibiotics is particularly necessary in septic shock in patients with neutropaenia, immunosuppressed and with diagnosed or suspected in-

The beneficial effects of combined antibiotic therapy on survival of patients with severe infections of various aetiologies were demonstrated in the recent meta-analysis [59]. The previous publications showed the benefits of this antibiotic therapy only in Pseudomonas aeruginosa infections [60]. Delayed anti-

The initial antibiotic therapy of severe infections is usually empiric. The choice of a suitable antibiotic for the treatment of nosocomial infections should be based on the epidemiological and bacteriological conditions in a given ward. In community-acquired infections, the knowledge of the regional or national epidemiological situation is needed [62]. Moreover, it is essential to determine quickly the sepsis-inducing strain susceptibility and MIC from the direct material obtained in selected cases [63].

The guidelines and recommendations of Polish and international scientific societies may be helpful in empiric therapy of infections (those with the clinical picture of severe sepsis or septic shock) [64–82]. Numerous recommendations for antibiotic treatment regard pharmacokinetic properties of antibiotics, dosing based on concentration measure-

the outcomes [2, 69, 70, 71, 72, 73, 77, 82]. In patients with severe sepsis and septic shock, the pharmacokinetics of antibiotics significantly changes, therefore the standard doses can be too low or too high [83, 84, 85, 86, 87]. This means that rational antibiotic therapy, often monitored by determinations of serum drug levels, is well grounded in this group of patients. To improve the clinical efficacy, the most recent recommendations consider the selected beta-lactam antibiotics and glycopeptides (vancomycin) administered in a prolonged or continuous infusion [70, 77, 82].

The duration of antibiotic therapy depends of the type of infection, pathogen and observed regression of clinical, laboratory and microbiological features of infection. The prolonged antibiotic therapy is often used in cerebral abscesses, endocarditis, inflammations of bones, joints and bone marrow, pyothorax, catheter-associated infections (when bacteraemia or fungaemia persists over 48–72 h after catheter removal), meningitis caused by Gram-negative bacteria (including Pseudomonas and Listeria). Considering the etiological factor, prolonged treatment should be used in infections caused by Nocardia, Mycobacterium, Chla-

Antibiotic therapy of abdominal infections caused by the identified microorganism should be limited to 4–7 days, unless the suitable control of the infection source has been achieved. Longer antibiotic therapy is not associated with better treatment outcomes [69]. Generally, antibiotic ther-

The decision about the withdrawal of treatment is based on the patient’s clinical state, subsidence of clinical symptoms, normalisation of laboratory results, including microbiological markers of infection. Procalcitonin (PTC) is one of the markers, which was found useful for the diagnosis of infections (its level is increased in bacterial, fungal and, protozoal infections, yet only to some extent) and for monitoring the effectiveness of therapy. Furthermore, the recent studies indicate its usefulness to make decisions about the withdrawal of therapy. The antibiotic withdrawal at PTC concentration decreased by 90% or more compared to the baseline value yet not before the day 3 (if baseline PTC < 1 ng mL⁻¹) or day 5 (if baseline PTC ≥ 1 ng mL⁻¹) shortens the antibiotic therapy by 3.5 days and ITU hospitalization by 2 days, compared to the control group [88]. The multi-centre randomised study demonstrated that the concentration of PCT < 0.5 ng mL⁻¹ and its decrease by over
80% in comparison with the peak (maximum) value after at least the 3-day therapy resulted in 2.7 times shorter treatment, lower antibiotic therapy costs and similar 28- and 60-day mortality rates [89]. The antibiotic therapy was significantly shorter in the PCT group (5.9 ± 1.7 days) than in the control group (7.9 ± 0.5 days) when discontinued once the clinical and laboratory symptoms had subsided and the concentration of PCT had been < 1 ng/mL or > 1 ng/mL, and had decreased to 25–35% compared to the baseline value during three consecutive days [90].

References


