ANTIBIOTIC TREATMENT OF CRITICALLY ILL PATIENTS WITH SEPSIS: FROM PK/PD TO NOVEL DRUGS

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Abstract

Early detection of sepsis and its severity is critical for initiating proper therapy, including antibiotics, as soon as possible to maximize survival chances. Understanding the pathophysiological changes in septic shock that impact antimicrobial pharmacokinetics and pharmacodynamics (PK/PD), understanding the basics of PK/PD, and knowing PK-PD strategies in septic shock patients are all critical for appropriate therapy. By definition multi-drug resistant (MDR) microorganisms are those with acquired non-susceptibility to at least one agent in three or more antimicrobial categories. In the race between bacteria and novel antibiotics development, unfortunately, the number of new antibiotics/indications is not keeping pace with resistance and needs, especially for MDR Gram-negative microorganisms. When we fast forward to the approved antibiotics in the last five years, the list is rather short. Lefamulin is a novel pleuromutilin antibiotic that demonstrates activity against most Gram-positive pathogens. Cefiderocol is an injectable siderophore cephalosporin. Like other β-lactam antibiotics, it inhibits Gram-negative bacterial cell wall formation by binding to penicillin-binding proteins. Imipenem/cilastatin/relebactam is a new β-lactam/β-lactamase inhibitor combination with activity against MDR Gram-negative bacteria, including many CRE but excluding Metallo-β-lactamase (MBL)-producing *Enterobacterales* and CRAB. Those three antibiotics were FDA - approved in 2019 and European Medicines Agency (EMA) approved them in 2020. Plazomicin is a new semisynthetic aminoglycoside with activity against several MDR Gram-negative organisms, including CRE (FDA-approved in 2018). Meropenem-vaborbactam is a fixed-dose combination product of a carbapenem and a cyclic boronic acid β-lactamase inhibitor with potent activity against resistant Gram-negative bacteria like *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE; it is inactive against CRAB (FDA-approved in 2017; EMA-approved in 2018). Eravacycline is a new completely synthesized fluorocycline. It has a high level of effectiveness against Gram-positive and Gram-negative bacterial strains that have developed tetracycline-specific resistance mechanisms; it is inactive against *Pseudomonas aeruginosa* (FDA- and EMA-approved in 2018). Concluding this list of recently approved antibiotics is omadacycline, novel aminomethylcycline and a derivative of minocycline, with a chemical structure similar to tigecycline. Like other tetracyclines, omadacycline inhibits bacterial protein synthesis and possesses broad-spectrum antibacterial activity against Gram-positive and Gram-negative aerobic, anaerobic, and atypical bacteria including CRAB. It is inactive against *Pseudomonas aeruginosa* (FDA-approved in 2018). There are three novel carbapenems sulopenem, tebipenem pivoxil hydrobromide and benapenem. There is a group of antibiotics in phase III clinical trials: the combination aztreonam/avibactam, sulbactam/durlobactam, cefepime/enmetazobactam, cefepime/

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zidebactam, cefepime/aniborbactam. An interesting approach to antimicrobial treatment is antimicrobial drug repurposing. Drug combinations could be a strategy to extend the life of antibiotics in the XXI century due to the multi-targeting mechanisms of agents. New active substances are urgently required to stop the spread of antibiotic-resistant bacteria. However, it could be a rather cumbersome and expensive procedure. Antimicrobial misuse and/or overuse contribute greatly to this very important global healthcare problem.

Keywords: critically ill, septic shock, novel antibiotics, combined therapy, multi-drug resistant bacteria

Introduction

The term "sepsis" was first used in a medical context in Greek texts by Homer over 2500 years ago, deriving from the Greek word for "putrefaction". Hippocrates, Aristotle, Plutarch, and Galen, among others, used the term with a similar connotation of decay or disintegration. These ancient Greek doctors had limited knowledge of infectious processes, yet they recognized sepsis as a cause of mortality. Early detection of sepsis and its severity is critical for initiating proper therapy, including antibiotics, as soon as possible to maximize survival chances. Sepsis still has a mortality rate of roughly 35% and septic shock has a mortality rate of around 60%[1].

Pharmacokinetics and pharmacodynamics (PK/PD) considerations for antibiotics in septic shock patients

Understanding the pathophysiological changes in septic shock that impact antimicrobial pharmacokinetics and pharmacodynamics (PK/PD), understanding the basics of PK/PD, and knowing PK-PD strategies in septic shock patients are all critical for appropriate therapy. Septic shock leads to a significant pathophysiological derangement resulting in reduced antibiotics exposure. Yet another problem is regarding dosing regiments. During the first few phases of the clinical trials data are collected from healthy subjects in uncomplicated infections. Also, there is high inter - and intra-patient variability regarding PK/PD in critically ill septic patients, resulting in underdosing which leads to therapeutic failure and bacterial resistance. The ultimate goal is PK/PD dose optimization which improves outcomes and reduces mortality in critically ill patients. The spectrum of critical illness-related altered pathophysiology and its effects on drug concentrations has been extensively investigated by Jason Roberts, Jeffrey Lipman and co-workers[2, 3]. A hyperdinamic phase of critical illness is characterized by increased cardiac output leading to increased clearance (CL) and decreased plasma concentrations. Altered fluid balance manifests as third spacing (capillary leak) and/or altered protein binding. In these circumstances, the volume of distribution (Vd) increases while plasma concentrations decrease. "Normal" plasma concentrations require unchanged Vd and CL with no organ dysfunction. The other part of the spectrum encompasses renal and/or hepatic dysfunction, with increased Vd but decreased CL leading to increased plasma concentrations. Finally, in the case of organ support (renal replacement therapy – RRT and/or extracorporeal membrane oxygenation – ECMO), there is increased Vd with unknown CL so plasma concentrations could increase or decrease. There is a big proportion of critically ill patients (trauma patients, those with neurological issues, etc.) with augmented renal clearance (> 130 mL/min) and decreased plasma concentrations who are at risk of underdosing. This is of special concern when hydrophilic antibiotics with low Vd, such as β-lactams and aminoglycosides, are administered. There are several concurrent conditions leading to increased Vd and decreased plasma concentrations of these drugs in critically ill patients: 1) systemic inflammation leading to capillary leak; 2) high cardiac output coupled with intravenous fluids administered as a volume replacement therapy; 3) augmented renal clearance; 4) post-surgical drains often present in this patient population; 5) hypoalbuminemia with consequently decreased protein binding. Underdosing promotes bacterial resistance.

Pharmacodynamic kill characteristics put antibiotics in three large groups. Time (T) dependent antibiotics are penicillins, cephalosporins, carbapenems, linezolid, clarithromycin and clindamycin. The optimal PK/PD index for these antibiotics is T > MIC (minimal inhibitory concentration); eg. 40-100% T > MIC for β-lactams. Here, the objective is to maximize the duration of exposure with frequent administration or prolonged infusion dosing. Concentration (C) dependent antibiotics are aminoglycosides, metronidazole and daptomycin with optimal PK/PD index being Cmax: MIC; eg. Cmax: MIC 8-10 for aminoglycosides. Here, concentration should be maximized with infrequent (once daily) administration of high doses. The third group consists of antibiotics that are concentration dependent with time dependence: fluoroquinolones, azithromycin, glycopeptides, tetracyclines and tigecycline. The therapeutic goal of these antibiotics is to maximize the amount of drug exposure by administering high total daily dose[4]. Strategy for β-lactams in the treatment of critically ill patients could encompass loading dose plus prolonged (continuous or extended) infusions. The loading dose is essential in achieving therapeutical serum concentrations in order to compensate for increased Vd. Continuous infusions would, theoretically, cover 100% of the dosing interval while extended infusions would cover 40-50% of the dosing interval. Ideally, therapeutic drug monitoring (TDM) allows confirmation of adequate antibiotic levels for optimal treatment and avoidance of toxicity or adverse events. In real life, it is not readily available for all

antibiotics, it could be a rather cumbersome and expensive procedure.

Finally, in critically ill septic patients, "one-dose fits all" therapeutic approach is not appropriate. Also, clinical experience demonstrated that dose of β-lactams should not be adjusted to renal function in the first 24 hours even in patients with acute kidney injury because aforementioned pathophysiological derangements will outweigh any increased concentration concerns by far.

Resistance to antibiotics

In the medical literature, several distinct definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan drug-resistant (PDR) microorganisms are used to define the various patterns of resistance. MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates are only susceptible to one or two categories), and PDR as non-susceptibility to all agents in all antimicrobial categories[5]. The global threat of MDR is real. Local epidemiology variables should be taken into account and prevalence is high in many countries. XDR is emerging with exponential increase; it is mostly related to outbreaks. It is worrisome that there are limited therapeutic options when it is out of control. PDR threat might be the start of the "post-antibiotic era", and it might come in the near future, unfortunately it is the reality for some countries. In the race between bacteria and novel antibiotics development, unfortunately, the number of new antibiotics/indications are not keeping pace with resistance and needs, especially for MDR Gram-negative microorganisms.

The development of antibiotics through history

Penicillin has been developed in the late 1920s, cephalosporin in the late 1940s, carbapenem and fluoroquinolones in the late 1970s. But there has been a discovery void over the last 30 years, with no major new types of antibiotics being developed. The majority of the new antibiotics represent modifications to existing chemical structures, trying to tackle the specific mechanisms of resistance, rather than new drug classes. Since 2010, the Food and Drug Administration (FDA) has authorized just 17 new systemic antibiotics and 1 related biologic agent. Fourteen of these medications were authorized for common bacterial infections, one for *Clostridioides difficile* infection (CDI), one to prevent CDI recurrence, and two for drug-resistant tuberculosis[6]. Yet, none of these new antibiotics was specifically approved for MDR infections caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) or carbapenem-resistant *Enterobacteriaceae* (CRE). The difficulty in treating CRAB infections stems from a strong resistance profile that leaves just a few medicines with questionable efficiencies, such as colistin and tigecycline, accessible[7]. Antibiotic choices for CRE are still quite restricted, with polymyxins, tigecycline, fosfomycin, and aminoglycosides serving as the mainstays of therapy[8].

World Health Organization (WHO) regards Gram-negative bacilli (GNBs) to be of critical priority, most notably CRAB, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and 3rd generation cephalosporin-resistant and carbapenem -resistant *Enterobacteriaceae* (CRE). Penicillin was accidentally found over a century ago on a bacterial culture plate infected with mold. The capacity of penicillin to destroy a wide variety of bacterial species was what made it such a groundbreaking medicine. Because of its broad spectrum of action, it may be utilized to treat a wide range of infections, even those where the causative agent remained unknown[9]. The potential of pathogenic bacteria to acquire and evolve an assortment of antibiotic resistance mechanisms has long hindered the use of life-saving medications. The antibiotic resistome, which is the total of various resistance pathways, poses a severe challenge to antibiotic discovery, development, and usage. Traditional approaches to combating resistance, such as semisynthetic modification of naturally occurring antibiotic scaffolds, development of adjuvant therapies that overcome resistance mechanisms, and total synthesis of new antibiotics and their analogues, are based on the study and understanding of the underlying molecular mechanisms in the resistome as well as diversity of resistance mechanisms. So, this would represent resistance-guided antibiotic discovery[10].

New antibiotics in the last five years

When we fast forward to the approved antibiotics in the last five years, the list is rather short. Lefamulin[11] is a novel pleuromutilin antibiotic that demonstrates activity against most Gram-positive pathogens (FDA-approved in 2019; European Medicines Agency (EMA)-approved in 2020). Strategies to tackle β-lactamases would be based on synthesis of new β-lactam compounds refractory to hydrolysis by these enzymes, like cefiderocol, which overcomes different resistant mechanisms prevalent in Gram-negative bacteria.

Cefiderocol[12] is an injectable siderophore cephalosporin. Like other β-lactam antibiotics, it inhibits Gram-negative bacterial cell wall formation by binding to penicillin-binding proteins; however, it is unusual in that it reaches the bacterial periplasmic space as a consequence of its siderophore-like characteristic and has greater stability to β-lactamases (FDA-approved in 2019; EMA-approved in 2020). In the CREDIBLE-CR trial, a randomized, open-label, multicenter, parallel-group, pathogen-focused, descriptive, phase 3 study, authors assessed the efficacy and safety of cefiderocol or best available therapy (BAT) for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria[13]. A total of 150 patients with carbapenem-resistant

Gram-negative bacteria were enrolled. Participants were randomly allocated (2:1) to receive either a 3 h intravenous infusion of cefiderocol 2 g, every 8 h or the best available treatment (pre-specified by the investigator before randomization and consisting of a maximum of three medicines) for 7-14 days. This trial demonstrated that cefiderocol is a viable option, with similar clinical and microbiological efficacy to the best available therapy, for the treatment of carbapenem-resistant infections in patients with limited treatment options. The cefidecorol approach is less toxic than, for example, colistin received in over 50% of patients in the best available treatment group.

Imipenem/cilastatin/relebactam[14] is a new β-lactam/β-lactamase inhibitor combination with activity against MDR Gram-negative bacteria, including many CRE but excluding Metallo-β-lactamase (MBL) - producing *Enterobacterales* and CRAB (FDA - approved in 2019; EMA - approved in 2020). Plazomicin[15] is a new semisynthetic aminoglycoside with activity against several MDR Gram-negative organisms (better for lactose-fermenting), including CRE (FDA - approved in 2018). Meropenem-vaborbactam[16] is a fixed-dose combination product of a carbapenem and a cyclic boronic acid β-lactamase inhibitor with potent activity against resistant Gram-negative bacteria like *Klebsiella pneumoniae carbapenemase* (KPC) - producing CRE; it is inactive against CRAB (FDA-approved in 2017; EMA-approved in 2018).

Eravacycline[17] is a new completely synthesized fluorocycline with a tetracyclic core scaffold and unique alterations in the tetracyclic D-ring. It has a high level of effectiveness against Gram-positive and Gram-negative bacterial strains that have developed tetracycline-specific resistance mechanisms; it is inactive against *Pseudomonas aeruginosa* (FDA - and EMA-approved in 2018). Concluding this list of recently approved antibiotics is omadacycline[18], novel aminomethylcycline and a derivative of minocycline, with a chemical structure similar to tigecycline. Like other tetracyclines, omadacycline inhibits bacterial protein synthesis and possesses broad-spectrum antibacterial activity against Gram-positive and Gram-negative aerobic, anaerobic, and atypical bacteria including CRAB. It is inactive against *Pseudomonas aeruginosa* (FDA-approved in 2018). The global spread of MBL is an urgent, yet unattended public health threat.

Antibiotics in clinical trials

There is a group of antibiotics in phase III clinical trials or with the application for marketing authorization (New Drug Application - NDA in the USA or Marketing Authorization Application - MAA in the European Union). So, both NDA and MAA do represent applications filed to obtain the marketing permission. Upon receiving the approval, medicine can be launched on the market. Aztreonam is an older β-lactam (monobactam) with the ability to withstand hydrolysis by MBL carbapenemases. However, since many MBL-producing strains co-produce enzymes that could hydrolyze aztreonam (serine β-lactamases such as extended spectrum β-lactamases - ESBL and AmpC β-lactamases – AmpC etc.), a robust β-lactamase inhibitor such as avibactam, not susceptible to hydrolysis by serine β-lactamases, could be given as a partner drug. It should be noted that plasmids containing MBL genes generally also harbor genes that encode several of these other β-lactamases. The combination aztreonam/avibactam[19] appears to be a promising option against MBL-producing bacteria (especially *Enterobacterales*, much less for *Pseudomonas aeruginosa*). Authors of a recently published study[20] demonstrated that aztreonam/avibactam showed potent activity against a large collection of *Enterobacterales* isolated from Western and Eastern European medical centers, including MBL-producing strains. This drug combination inhibited 99.9% of *Enterobacterales* at ≤ 8 mg/L while resistance was extremely rare. Yet, the recent emergence of aztreonam/avibactam resistance in carbapenemase-producing *Escherichia coli* was detected in Germany[21]. Durlobactam is a new broad-spectrum inhibitor of serine-type β-lactamases that restores sulbactam intrinsic (SUL) activity against *Acinetobacter baumannii*. The sulbactam/durlobactam (SD) combination recently completed Phase 3 testing in the worldwide ATTACK trial[22]. *In vitro* combination of these two β-lactamase inhibitors demonstrated potent activity against MDR CRAB clinical strains. More than half (54.6%) of these isolates were resistant to colistin. The susceptibility of CRAB in vitro was 96.9%[23]. Phase I and II trials of SUL/DUR combination demonstrated good lung concentration and activity improved with the addition of imipenem. Also, prolonged IV infusion was proposed.

Cephalosporin of 4th generation cefepime is being investigated in combination with either one of three novel β-lactamase inhibitors zidebactam, taniborbactam, and enmetazobactam against a multicenter collection of carbapenemase-producing *Enterobacterales*[24]. Cefepime/enmetazobactam is a novel β-lactam/β-lactamase inhibitor combination and a potential empirical therapy for resistant Gram-negative infections[25]. This combination has adequate intrapulmonary penetration and potential role as carbapenem-sparing regimen for ESBL-producing *Enterobacterales*; it is not for carbapemen non-susceptible strains. A very interesting novel β-lactamases inhibitor is zidebactam. It is first in class β-lactam enhancer with intrinsic β-lactam activity by binding to bifunctional penicillin-binding protein (PBP2) of *Enterobacterales, Pseudomonas aeruginosa* and *Acinetobacter baumanii*[26]. Taniborbactam, an investigational β-lactamase inhibitor active against both serine - and metallo-lactamases, is being developed in tandem with cefepime (2 g cefepime/0.5 g taniborbactam) to treat severe infections caused by multidrug-resistant Gram-negative bacteria[27].

Finally, there are three novel carbapenems in this group of antibiotics. Sulopenem is an intravenous and oral synthetic thiopenem β-lactam that possesses *in vitro* activity against fluoroquinolone-resistant, extended spectrum β-lactamases (ESBL)-producing, multidrug-resistant (MDR) *Enterobacterales*[28]. It is not active against *Pseudomonas*

aeruginosa and *Stenotrophomonas maltophilia*. Tebipenem pivoxil hydrobromide is an orally bioavailable prodrug with tebipenem being active form. It was non-inferior to intravenous ertapenem in the treatment of complicated urinary tract infection and acute pyelonephritis and had a similar safety profile[29]. Tebipenem pivoxil is the first orally available carbapenem antibiotic[30], thus far it is not of crucial importance for critically ill patients. Benapenem is well tolerated, once daily IV administered novel carbapenem[31] with activity against ESBL-producing *Enterobacterales*. Phase II/III trial (NCT04505683) of benapenem versus ertapenem IV for complicated urinary tract infections/acute pyelonephritis is completed with pending results.

Butler and colleagues recently published excellent analysis of the antibiotics in any of the phases of clinical trials[32]. There have been 12 new antibacterial medications authorized worldwide since 2017. However only vaborbactam belongs to a new antibacterial class. Cefiderocol, a cephalosporin derivative with an iron-chelating siderophore that enhances Gram-negative bacteria cell entrance, is also novel. There were 76 antibacterial drugs in clinical trials, including 28 in phase 1, 32 in phase 2, 12 in phase 3, and 4 awaiting regulatory approval. The number of new antibiotics/indications is not keeping up pace with the resistance development and needs of patients. The vast majority of novel approved antibiotics, as well as those in the late stage of clinical development, represent modifications to existing chemical structures rather than new drug classes and unique mechanism of action. The current unmet medical need is for new drugs to treat MDR *Acinetobacter baumanii* (eg. CRAB) and *Pseudomonas aeruginosa* (eg. CRPA) infections.

New approaches in the application of antibiotics

An interesting approach to antimicrobial treatment is antimicrobial drug repurposing. Repurposing the veterinary antibiotic apramycin for antibacterial and antibiofilm activity against *Pseudomonas aeruginosa* from cystic fibrosis patients[33] supported further pharmacokinetic and pharmacodynamic research and the rationale to repurpose apramycin, a veterinary aminoglycoside, for treating lung infections in these patients. In another study, apramycin demonstrated best-in-class activity against a panel of Gram-negative bacilli isolates with resistances to other aminoglycosides, carbapenems, the third generation cephalosporins and colistin[34]. A panel of 470 Gram-negative bacilli comprising *Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Acinetobacter spp.* and *Pseudomonas aeruginosa* were selected in this research.

Another approach to antimicrobial drug repurposing is making drugs new out of old to treat other diseases and pathogens. For example, the anthelmintic drug niclosamide selectively synergized with the lipopeptide antibiotic colistin against colistin-susceptible but more importantly against colistin-resistant Gram-negative bacilli[35].

BamA is a β-barrel, outer membrane protein found in Gram-negative bacteria that serves as the major and essential component of the β-barrel assembly machinery (BAM) complex. It inserts proteins into the outer membrane, which makes it an attractive target due to its surface location. *Photorhabdus australis*, a nematode gut microbiome symbiont, produces darobactins that target BamA. Very recently, Miller et al.[36] through computational search for genes only distantly related to the darobactin, identified dynobactin A, a novel peptide antibiotic from *Photorhabdus australis*. Dynobactin is structurally unrelated to darobactins, but also targets BamA. Dynobactin demonstrated efficacy in a mouse systemic *Escherichia coli* infection. Gepotidacin[37] is a new, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial deoxyribonucleic acid (DNA) replication through a distinct mode of action, conferring efficacy against most strains of target pathogens in urinary tract infections (*Escherichia coli, Staphylococcus saprophyticus*) even those resistant to conventional antibiotics. This new antibiotic will likely be studied and used to treat more serious infections.

Klebsiella pneumoniae is the cause of a number of serious illnesses. Many *Klebsiella pneumoniae* strains are antibiotic resistant, necessitating the development of novel antibacterial compounds. The pathogenicity of *Klebsiella pneumoniae* is primarily dependent on its capacity to evade phagocytosis and intracellular death by phagocytic cells. Interfering with these escape mechanisms might help to reduce bacterial pathogenicity and fight infections. A team from the University of Geneva has discovered that edoxudine, an anti-herpes molecule discovered 60 years ago, weakens the protective surface of *Klebsiella* bacteria and makes them easier to eliminate for immune cells[38]. To determine whether or not the bacteria were weakened, investigators used an experimental model with surprising characteristics: the amoeba *Dictyostelium*. This single-cell organism feeds on bacteria by capturing and ingesting them, using the same mechanisms that immunocompetent cells use to kill pathogens. This amoeba was genetically modified so that it could be determined whether the bacteria it encountered were virulent or not. This system then enabled investigators to test thousands of molecules and identify those that reduced bacterial virulence. Authors then opted for a quicker and safer strategy: reviewing existing drugs to identify possible new therapeutic indications. By altering the surface layer that protects the bacteria from their external environment edoxudine makes it vulnerable. Also, unlike antibiotics, edoxudine does not kill the bacteria, which limits the risk of developing resistance. Investigators concluded that sufficiently weakening the bacteria without killing them is a subtle strategy but one that could prove to be a winner in the short and long terms.

Combined antibiotic therapy

By definition, combined antibiotic therapy leads to extended spectrum when two antibiotics are used and thereby increases the chances of targeting an unknown causative organism. Then there is extended spectrum with partial combination with an overlap in targeting bacteria but then again also widening the spectrum. Combined therapy, or dual action therapy, consists of two antibiotics targeting the same bacteria. Theoretical advantages of combined therapy would encompass broader empirical coverage, synergistic effect that is more effective killing of the causative organism and decreased risk of development of resistance since dead bugs do not mutate. However, there are theoretical disadvantages of using combined antibiotic therapy. Here, increased risk of toxicity, increased exposure to antibiotics driving resistance, collateral damage to commensal flora because the body consists of more bacteria than cells and increased costs would be included.

The question is why is it so difficult to demonstrate any difference in the outcomes of clinical trials? There are patient versus microbiological-centered outcomes. Patient-centered outcomes are mortality, morbidity (eg. renal insufficiency or *Clostridium difficile* infection) or length of stay (LOS), while microbiology-centered outcomes are clinical cure, eradication and resistance development.

Antibiotic resistance is a global and growing clinical iss-ue. Given the scarcity of antibacterial medication development, combined treatment has emerged as a potential technique for combating multidrug-resistant microorganisms. Through independent, synergistic, or even antagonistic effects, antibacterial combinations may increase antibiotic effectiveness and reduce antibacterial resistance[39].

The development of novel antibiotics is a time-consuming process, due to the strict chemical, biological, and pharmacological requirements for efficient antibiotic medications. Antibiotic combinations, as well as antibiotic combinations with non-antibiotic activity-enhancing substances, provide a promising technique for combating the widespread rise of antibiotic-resistant bacteria. Therefore, drug combinations could be a strategy to extend the life of antibiotics in the XXI century[40]. Multi-targeting agents might include inhibition of efflux pumps, increasement of membrane permeability, inhibition of enzyme modifications or degradation and allosteric binding to the target.

There are common assumptions about the benefits of combined therapy on patient-centered outcomes. Does pathogen burden kill patients or is it the dysregulated immune response to infection that kills patients? The dysregulated immune response is in linear relationship with the bacterial load and pathogen clearance is faster with two drugs compared to one are another two assumptions. Also, there is the question of two antibiotics being able to arrest the inflammatory cascade more rapidly and effectively than one. Finally, another question is do the theoretical benefits of treating with two antibiotics outweigh the increased risk of adverse effects that comes with exposing patients to two drugs rather than one. There is a viewpoint that monotherapy is adequate for septic shock due to Gram-negative organisms[41]. Uncontroversial combined therapy is regarding broadening the spectrum, in treatment of tuberculosis and HIV. An example of debated combined therapy would be treatment of community-acquired pneumonia (CAP) in terms of whether or not coverage for atypical pneumonia should be implemented. Authors of real-life DIANA study regarding antimicrobial de-escalation (ADE) in the critically ill patients and assessment of clinical cure, demonstrated that ADE was infrequently applied in critically ill-infected patients[42]. DIANA sub-study included 1.454 critically ill patients treated with empirical antibiotic therapy in 28 countries, out of which 22% with septic shock. It was shown that 58% of patients were treated with monotherapy while 42% were treated with combination therapy. Around 50% of these patients were treated with Gram-positive double coverage and/or extended spectrum, around 30% were treated with Gram-negative combined therapy, around 25% were treated with extended spectrum for atypical pathogens and around 3% received combined therapy for anaerobes.

Latest recommendations from Surviving Sepsis Campaign, from 2021, for treatment of Gram-negative sepsis, suggest using double Gram-negative coverage for patients with high risk for MDR pathogens and not using double Gram-negative coverage for patients with low risk for MDR microorganisms[43]. It should be noted that this is a weak recommendation with very low quality of evidence. Excellent systematic review with meta-analysis and trial sequential analysis regarding empirical mono-versus combined antibiotic therapy in adult critically ill patients with severe sepsis was performed by Sjövall et al[44]. Ten trials with 2.276 patients were included in the analysis. In adult ICU patients with severe sepsis, there were no differences in mortality or other patient-important outcomes between empirical mono- vs. combined antibiotic treatment. The amount and quality of data was low, and there was no strong evidence for the benefit or harm of combined therapy. In AMINOLACTAM study, impact of the inclusion of an aminoglycoside to the initial empirical antibiotic therapy for Gram-negative bloodstream infections (BSI) in hematological neutropenic patients was investigated[45]. Regarding the outcome of such treatment, 7-day outcome was improved but 30-day outcome was not improved although there was tendency toward lower mortality at 30 days with inclusion of an aminoglycoside therapy in these patients. In addition, aminoglycoside use was not significantly associated with renal function impairment. Antibiotic treatment with one single dose of gentamicin at admittance in addition to a β-lactam antibiotic in the treatment of community-acquired bloodstream infection with sepsis in a retrospective study[46] demonstrated additional value because it was associated with a lower risk of mortality and was not associated with acute kidney injury. The authors concluded that this antibiotic regimen

might be used instead of broad-spectrum antibiotics to treat community-acquired sepsis.

As long as the causative pathogen is covered with a single empirical therapy and this therapy is given in a timely manner and with adequate dosing, additional agents will most likely not give any additive benefits. In some difficult to treat infections (due to pathogen or infectious focus- necrotizing soft tissue infection) combined therapy for synergistic effect might be beneficial. The use of a short course of aminoglycoside in sepsis is still debatable.

With present diagnostic tools, early diagnosis of sepsis is difficult, resulting in $27 billion in yearly costs in the United States, with high related mortality[47]. Therefore, crucial questions like whether patients infected (or there is a systemic inflammation for instance) and can it be treated with antibiotics still remains difficult to answer. Some biomarkers can be used to support clinical decision-making. Empirical antibiotics are necessary, but improved detection and identification may increase precision. This may turn into clinical and cost-benefit if antibiotic stewardship is practiced.

Conclusion

The WHO refers to the steadily increasing number of bacteria that are resistant to antibiotics as a "silent pandemic". The situation is made worse by the fact that there haven't been many new drugs introduced to the market in recent decades. WHO review of antimicrobial resistance (AMR) suggests that there would be 10 million deaths by year 2.050 because of AMR, which is greater than cancer if the trajectory of AMR continues as it is currently. Even now, not all infections can be adequately treated, and patients still run the risk of harm from routine interventions. New active substances are urgently required to stop the spread of antibiotic-resistant bacteria. Antimicrobial misuse and/or overuse contribute greatly to this very important global healthcare problem.

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