Antimicrobial Treatment of *Pseudomonas aeruginosa* Severe Sepsis

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Pseudomonas aeruginosa is a pathogen often encountered in a healthcare setting. It has consistently ranked among the most frequent pathogens seen in nosocomial infections, particularly bloodstream and respiratory tract infections. Aside from having intrinsic resistance to many antibiotics, it rapidly acquires resistance to novel agents. Given the high mortality of pseudomonal infections generally, and pseudomonal sepsis particularly, and with the rise of resistant strains, treatment can be very challenging for the clinician.

Pseudomonas aeruginosa | severe sepsis | antibiotics | antimicrobial resistance

1. Empirical Antimicrobial Therapy

EAT in sepsis should consider the patient's allergies, comorbidities, the primary site of infection, prior antibiotic exposure, as well as local susceptibility patterns [1]. AMR should be highly suspected if there is recent admission to a hospital unit where prevalence of MDR-PA is greater than 20% or if the patient has received antipseudomonal beta-lactam antimicrobials within the past three months [2]. Although some studies reported trends towards decreased resistance of *P. aeruginosa* [3], low and middle income countries (LMICs) still suffer from a high burden of AMR [4]. The CDC reports that 32,600 cases of MDR-PA infections occurred in patients hospitalized in the United States in 2017, resulting in 2700 deaths [5]. For *P. aeruginosa*, MDR is defined as resistance to at least one agent in three or more antibiotic classes, extensive drug resistance (XDR) is defined as resistance to at least one agent in all but two or fewer antibiotic classes, and pan-drug resistance (PDR) is non-susceptibility to all agents [6]. Most recently, it was suggested to label MDR-PA as difficult to treat (DTR) when it is resistant to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin and levofloxacin [7][8].

Combination therapy in *P. aeruginosa* is often used to decrease the risk of inadequate EAT by combining drugs with multiple mechanisms of action. In a recently published multicenter retrospective study including 1017 neutropenic patients with *P. aeruginosa* bacteremic pneumonia, inappropriate EAT was given to 23% of patients and was associated with infection with MDR-PA. Additionally, inappropriate EAT was associated with increased 30-day mortality while appropriate EAT was independently associated with improved survival [9]. No consensus has been reached regarding the use of empirical combination versus monotherapy in *P. aeruginosa* sepsis, mainly due to the lack of robust prospective studies to provide strong levels of evidence [10]. In fact, a prospective study found no differences in outcomes between patients who received empirical combination antibiotics when compared to monotherapy [11]. A meta-analysis that included 1721 patients showed no difference in mortality among patients with pseudomonal infections who were treated empirically with beta-lactam monotherapy or combination therapy

with the addition of an aminoglycoside (AG) or a fluoroquinolone (FQ) [12]. Furthermore, a Cochrane research that included 69 randomized controlled trials (RCTs) with a total of 7863 patients comparing beta lactam monotherapy and combination with an AG in the management of sepsis showed no difference in mortality in the *P. aeruginosa* subgroup analysis and significantly increased nephrotoxicity with combination therapy [13]. Moreover, a post hoc analysis of 593 patients with *P. aeruginosa* bacteremia showed no benefit of empiric combination therapy [14] and another meta-analysis of 4980 patients showed no difference in mortality, microbiological, or clinical cure when using empirical combination vs. monotherapy for patients with *P. aeruginosa* BSI or pneumonia [15]. On the other hand, a retrospective cohort study by Micek et al. including 305 patients with *P. aeruginosa* BSI showed that using combination therapy while awaiting for identification and susceptibility testing decreased the risk of inadequate EAT from 79.4% to 65.5% (*p*-value = 0.011). Additionally, mortality was significantly higher in patients who received inappropriate EAT (30.7% versus 17.8%, *p*-value = 0.018). In that study, inappropriate EAT, respiratory failure and septic shock were found to be independent risk factors for in-hospital mortality [16]. A recent meta-analysis of four studies that evaluated all-cause mortality (total of 148 patients), showed a significant decrease in mortality with combination therapy for severe infections caused by *P. aeruginosa* (OR 0.31, 95% CI 0.1–0.97, *p*-value = 0.045) [17].

Given the rise of AMR and the risk of inadequate EAT, combination empiric therapy should be highly considered in cases of severe sepsis [18]. The Surviving Sepsis campaign recommends combination empirical therapy during acute illness [19]. Two different mechanisms of action are preferred, typically a backbone beta-lactam (conventional or novel depending on risk of AMR) combined with an AG or a FQ [2][20]. Although one study suggested better outcomes when FQ was used instead of AG as a second agent [21], the choice of agent should be guided by local susceptibility patterns [2]. A retrospective cross-sectional analysis of blood and respiratory *P. aeruginosa* isolates from patients admitted to the ICU found that the combination with the highest susceptibility was piperacillin-tazobactam combined with an AG, while the combination with the lowest susceptibility was a carbapenem combined with a FQ [22]. Additionally, isolates were found to have less resistance to combinations with AG than those with FQ. A pharmacokinetic/pharmacodynamic (PK/PD) prospective randomized controlled trial suggested that a higher dose of amikacin (25 mg/kg) for patients with severe sepsis and at risk for *P. aeruginosa* infection was more likely to achieve an MIC that is closest to the EUCAST susceptibility breakpoint than standard dosing (15 mg/kg) [23]. Above all, the choice of empiric antimicrobial regimen should consider the potential for co-resistance to multiple first-line agents. For instance, a multinational microbiological study including 1783 isolates of MDR-PA from patients with *P. aeruginosa* BSI reported that co-resistance to many first-line antipseudomonal agents was very common, especially between piperacillin-tazobactam, meropenem and ceftazidime. Among antimicrobials that were included in the study, only Ceftolozane-tazobactam (C/T), a novel beta-lactam-beta-lactamase inhibitor combination, achieved significant additional activity against strains that exhibited resistance to one of the first-line agents [24]. Those findings suggest that C/T may be considered for empirical therapy if local rates of PA resistance to first-line agents is high. If combination empiric therapy is used, it is highly recommended prompt de-escalation once there is clinical improvement and susceptibility results are available. Additionally, although 40% of *P. aeruginosa* BSIs will have an unidentifiable origin, prompt source control is recommended when possible to improve patient outcomes [25][26].

2. Targeted Therapy for *P. aeruginosa* Sepsis

2.1. P. aeruginosa Sensitive to First Line Antipseudomonal Agents

P. aeruginosa is intrinsically resistant to several antibiotics due to the low permeability of its outer membrane, expression of various efflux pumps, and the production of antibiotic-inactivating enzymes such as inducible cephalosporinases. First-line beta-lactam agents for *P. aeruginosa* coverage include beta-lactam/beta-lactamase-inhibitor combinations (BL/BLI) (piperacillin-tazobactam and ticarcillin-clavulanate) and cephalosporins with antipseudomonal activity (ceftazidime, cefepime, and cefoperazone). Cefepime is the most commonly used beta-lactam antibiotic for *P. aeruginosa* [27]. Fluoroquinolones (ciprofloxacin and levofloxacin) remain currently the only oral treatment options for quinolone-sensitive *P. aeruginosa*. However, ciprofloxacin is superior to levofloxacin given the higher risk of emergence of quinolone-resistant *P. aeruginosa* with the use of levofloxacin [28]. Additionally, older FQ are less effective in acidic environments like UTIs [29]. Newer FQ such as finafloxacin and delafloxacin offer more activity in acidic environments but are yet to be widely available [30].

Second line agents for *P. aeruginosa* sepsis are carbapenems, including meropenem, imipenem, and doripenem. Meropenem is often preferred over imipenem given the latter's higher propensity to induce resistance during treatment [31]. Doripenem was shown to be more active in vitro against *P. aeruginosa* compared to meropenem and imipenem but this has not been proven in clinical studies [32][33]. Nonetheless, cephalosporins should be favored over carbapenems when applicable due to more potent activity and narrower spectrum [34] as well as less propensity to select for future resistance [35].

Other agents include the monobactam class (aztreonam) which can be used as an alternative for patients with penicillin allergy. Gentamicin, tobramycin, and amikacin are all AG that can be active against *P. aeruginosa* but are not indicated as monotherapy except for UTIs, as they are associated with higher mortality rates [36]. In the case of severe sepsis, the pathophysiological shifts may lead to an increased volume of distribution and augmented renal clearance and may lead to suboptimal AG concentrations and potentially poorer outcomes [37]. For optimal coverage, researchers prefer tobramycin or amikacin over gentamicin [38]. Otherwise, plazomicin, a newer AG, was shown to be less effective and is currently only indicated in the treatment of UTIs [39].

Emergence of resistance during the course of treatment is a serious concern. Such is the case of a cohort of 271 patients with various *P. aeruginosa* infections receiving antipseudomonal antimicrobial therapy, where emergent resistance was reported in up to 10% of cases [35]. Additionally, standard susceptibility testing may not be as accurate in identifying resistance when hospitalization duration increases. This is likely due to development of resistance or acquisition of drug-resistant hospital-acquired strains, especially with prolonged stay in the ICU. Studies have indicated that initial antibiograms become unreliable as a predictor of susceptibility of *P. aeruginosa* after 1–2 weeks of hospitalization, particularly in the ICU, with a significant increase in MIC for multiple anti-pseudomonal agents [40][41]. Among conventional treatment agents, imipenem was the most likely to cause resistance emergence and ceftazidime was the least likely [35].

2.2. P. aeruginosa Resistant to First Line Therapy

P. aeruginosa can develop resistance through multiple mechanisms including selection of chromosomal mutations or horizontal acquisition of broad-spectrum resistance genes. Many resistance mechanisms are involved and include beta-lactamase production, AG-modifying enzymes, efflux pumps, porin loss, and various target site modifications [34]. Treatment options for CRPA is challenging given the variety of resistance mechanisms like the production of carbapenemases of different classes, outer membrane protein modification (OprD) or efflux pumps (MexAB, MexXY). Novel anti-pseudomonal drugs have been developed in response to this challenge to address the increase in resistance, which has been reported in up to 54% of nosocomial *P. aeruginosa* infections [42][43][44]. These include novel BL-BLI like C/T, ceftazidime/avibactam (CAZ/AVI), and imipenem-cilastatin/relebactam (IMI/REL) or novel cephalosporins like cefiderocol [1].

C/T has potent intrinsic anti-pseudomonal activity owing to its greater affinity to all essential penicillin-binding proteins (PBP) including PBP1b, PBP1c, and PBP3. Based on RCTs, the US Food and Drug association (FDA) and the European Medicines Agency (EMA) have approved the use of C/T in complicated intra-abdominal infections (IAIs), UTIs, and hospital-acquired pneumonia including ventilator-associated pneumonia (VAP) [45]. Subset analysis in the clinical trials showed that patients with *P. aeruginosa* had a favorable outcome compared to carbapenems in the HAP trial [46], carbapenems combined with metronidazole in the complicated IAI trial [47], and levofloxacin in the complicated UTIs trial [48]. CAZ/AVI is a novel BL/BLI combination approved by the FDA and the EMA for treatment of complicated UTIs, IAIs and infections with Gram negative resistant pathogens [49][50]. C/T and CAZ/AVI have been considered key therapeutic agents against resistant *P. aeruginosa* strains. However, since the commercialization of these agents, there has been emergence of resistance of *P. aeruginosa* following therapy, particularly with highly cephalosporin-resistant conferring mutations [51]. Data for treatment associated resistance in novel agents is still inconclusive, but it appears that the highest risk is with C/T and CAZ/AVI with common cross resistance to both agents [52][53]. Currently, real-world data is scarce and does not show superiority of an agent compared to another and therefore the choice of antimicrobial therapy should be based on the susceptibility profile which can vary according to the local epidemiology with regional variability [54]. Since the introduction of C/T, case reports and case series of MDR *P. aeruginosa* infections treated with C/T have demonstrated the clinical efficacy of this formulation, including its use to treat infections in critically ill patients, and those with cystic fibrosis [55][56]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recent guidelines for the treatment of infections caused by MDR Gram-negative bacilli suggest treatment with C/T as the single first choice for severe pseudomonal infections like severe sepsis [10]. As for the Infectious Diseases Society of America (IDSA), their guidelines recommend treatment with either C/T, CAZ/AVI, or imipenem/relebactam for infections with DTR *P. aeruginosa* outside the urinary tract [7]. In fact, although experience with CAZ/AVI in the management of *P. aeruginosa* infections is more limited, adding avibactam to ceftazidime has shown success in lowering MICs of many XDR *P. aeruginosa* isolates [57]. When considering XDR *P. aeruginosa*, an important concept is that although C/T is more likely to be active than CAZ/AVI, there are some C/T-resistant strains that can be susceptible to CAZ/AVI [58]. Therefore, in vitro susceptibilities to both agents should be obtained whenever possible.

Cefiderocol is a novel siderophore cephalosporin that can overcome efflux pumps. The IDSA recommends this agent as an alternative therapy when other novel BL/BLI agents are unavailable or if there is resistance or intolerance. A recent RCT compared the outcomes of patients with infections due to carbapenem-resistant bacteria treated with cefiderocol or best available therapy (BAT) [59]. Although the mortality rate was higher in the cefiderocol arm, the number of patients with *P. aeruginosa* infection was small, and increased mortality was only observed in patients with a mono- or polymicrobial infection including *Acinetobacter baumannii*. Furthermore, the results suggest that cefiderocol performed as well as BAT, but was not associated with significantly decreased mortality or reduced adverse events like what was reported from studies on newer BL/BLIs [60][61]. A recently published study of *P. aeruginosa* isolates resistant to C/T and CAZ/AVI concluded that cefiderocol was the most active agent against these isolates, with only one resistant clinical isolate (R504C substitution in PBP3) [51]. Imipenem-cilastatin/relebactam was also active against all isolates except two that carried the VIM-20 carbapenemase. In the same study, newer combinations such as cefepime/zidebactam and cefepime/taniborbactam displayed activity against most of the isolates, but resistance was observed in some strains with PBP3 amino acid substitutions and those that overexpressed mexAB-oprM or mexXY efflux pumps.

Evidence for the combination IMI/REL is derived from the RESTORE-IMI 1, a randomized controlled phase 3 trial, comparing IMI/REL to a combination of colistin and imipenem for patients with Gram-negative infections of which 77% were due to *P. aeruginosa*. There was a trend of lower mortality in the arm that was treated with the novel agent compared to combination therapy, but a significantly lower rate of adverse effects and nephrotoxicity [60]. In the subgroup analysis, patients with pneumonia as well as those with renal insufficiency had a higher mortality perhaps owing to lower concentration achieved with the given doses (86). As for meropenem/vaborbactam, it is not recommended given that the addition of vaborbactam was not found to restore susceptibility to meropenem-resistant strains [7].

Despite great outcomes associated with novel agents, these therapies remain inactive against most metallo-beta-lactamase-(MBL)-producing *P. aeruginosa* strains. The monobactam aztreonam is unique by demonstrating stability to hydrolysis by MBLs and may maintain activity against MBL-producing *P. aeruginosa* [62]. Many strains of MBL-producing *P. aeruginosa* will also contain mechanisms of resistance against aztreonam, such as increased expression of pseudomonas derived cephalosporinases (PDCs). Nevertheless, aztreonam is an attractive option in combination with CAZ/AVI for the treatment of infections caused by MBL-producing *P. aeruginosa* [63]. Cefiderocol has also shown activity against all carbapenemase classes including MBL but more clinical evidence is needed [64].

As for polymyxins (polymyxin B and colistin), the IDSA's latest guidelines for the treatment of DTR *P. aeruginosa* recommends against their use when novel options with less nephrotoxicity are available [7]. However, given the increase in resistance rates and scarcity of novel antibiotics in LMICs, colistin has been increasingly used. Studies have shown that colistin can be used as salvage therapy when options are limited [65], and that it can be associated with a lower expected incidence of nephrotoxicity than previously expected. However, renal function should be closely monitored during therapy with appropriate dose adjustments.

Fosfomycin is an interesting choice for DTR *P. aeruginosa* given that it retains activity against some XDR and PDR strains which may be useful especially in critically ill patients with severe sepsis [66]. A case series including 48 critically ill patients, of whom 17 had infection with MDR-PA and 10 with severe sepsis, evaluated the efficacy of intravenous fosfomycin mainly in combination with colistin. Patients who received fosfomycin were found to have an all-cause 28-day mortality of 37.5%. Additionally, adverse events were minor and included nausea and reversible hypokalemia while resistance emergence to fosfomycin was found in only 3 patients [67]. Another retrospective study comparing outcomes between patients with CRPA pneumonia receiving a combination of doripenem and colistin or doripenem and fosfomycin found similar outcomes between both groups; however, results should be cautiously interpreted given the small size of the study's population (49 patients) [67]. It should be noted that intravenous fosfomycin should not be given as monotherapy except in cases of uncomplicated UTI; otherwise, it should be given in combination with other agents for bacteremia, nosocomial pneumonia and complicated skin and soft tissue infection to avoid emergence of resistance [18].

While definitive combination therapy may exert a synergistic effect and possibly reduce the emergence of resistance, it can also result in increased side effects and unnecessary costs [34]. It has been previously discussed the lack of rigorous evidence regarding the efficacy and safety of empirical combination therapy. Similarly, the evidence concerning the efficacy and safety of definitive combination antimicrobial therapy is still inconclusive and guidelines are yet to make a specific recommendation regarding combination therapy once susceptibility results are available. A retrospective study of 187 patients with *P. aeruginosa* BSI found that there was significant decrease in mortality in patients treated with definitive combination therapy compared to monotherapy by multivariate analysis (HR 0.30, 95% CI 0.13–0.71, $p = 0.006$) [68]. On the other hand, many studies have found no differences in outcomes between patients who received definitive combination vs. monotherapy [11]. For example, a retrospective study including 183 patients with *P. aeruginosa* VAP found similar outcomes with combination vs. monotherapy [69]. Furthermore, a meta-analysis found no difference in mortality between combination and monotherapy for patients with *P. aeruginosa* infections [12]. Hence, a single agent (preferably a beta-lactam based on susceptibility profile) should be used for definitive antimicrobial therapy since continuing combination therapy is unlikely to have any added value once susceptibilities are available [20].

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