Treatment for *Pseudomonas aeruginosa* Infections

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Pseudomonas aeruginosa is a ubiquitous Gram-negative bacterium renowned for its resilience and adaptability across diverse environments, including clinical settings, where it emerges as a formidable pathogen. Notorious for causing nosocomial infections, *P. aeruginosa* presents a significant challenge due to its intrinsic and acquired resistance mechanisms.

Pseudomonas aeruginosa resistance combination therapy TOL-TZB CAZ-AVI FDC

1. Introduction

Pseudomonas aeruginosa, a ubiquitous Gram-negative bacterium from the Pseudomonadaceae family, has garnered considerable attention for its resilience and adaptability in many environments. Notably, it bears a relatively larger genome, ranging from 5.5 to 7 Mbp, giving it a remarkable metabolic versatility and enabling it to thrive and adapt to diverse environmental shifts, thereby contributing to its survival in varied habitats, including water, soil, and associations with animals [1][2]. Furthermore, the bacteria's widespread presence in water sources, such as tap water and hand soap dispensers, has been associated with hospital outbreaks, indicating a pressing need for stringent hygiene measures and environmental control [3][4]. *P. aeruginosa* genotypes analysis has identified household environments, such as sinks and nebulizers, as potential sources of infection, necessitating vigilant monitoring and sanitation [3][4].

While *P. aeruginosa's* environmental tenacity is noteworthy, its role as an opportunistic pathogen has raised significant concerns, particularly in hospital settings [5]. It is notorious for causing nosocomial infections and ventilator-associated pneumonia, primarily affecting immunocompromised individuals, severe burn victims, and patients with underlying health conditions such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) [6][7][8][9][10]. In particular, *P. aeruginosa*'s ability to form biofilms, coupled with its intrinsic, acquired, and adaptive resistance mechanisms, has rendered it a formidable adversary in the clinical setting [11][12][13][14]. It exhibits resistance to many antibiotics, including aminoglycosides, fluoroquinolones, and β-lactams, through mechanisms such as low outer membrane permeability, the expression of efflux pumps, and the production of antibiotic-inactivating enzymes [11][15][16][17]. Acquired resistance through horizontal gene transfer and mutations,

along with adaptive resistance exemplified by biofilm formation and the emergence of persister cells, further complicate its treatment landscape [18].

Globally, the incidence of multidrug-resistant (MDR.) *P. aeruginosa* has exhibited an alarming upswing, posing considerable challenges to public health and clinical treatment [19][20]. The European Centre for Disease Prevention and Control (ECDC) has reported a varying prevalence of MDR *P. aeruginosa*, with some regions witnessing a heightened occurrence, underscoring the geographical disparity and the necessity for region-specific interventions [21]. The global landscape is similarly marked by a heterogeneous distribution of MDR strains, emphasizing the criticality of continuous surveillance and adaptive strategies to curb the spread of resistance [22]. The escalating challenge posed by *P. aeruginosa* has been accentuated by the World Health Organization (WHO), which has categorized carbapenem-resistant strains as being in critical need of new antibiotics [23]. The emergence of these strains has been associated with elevated morbidity and mortality, amplifying the urgency for innovative and effective therapeutic approaches [24]. These strategies include novel antibiotics and non-antibiotic therapeutic options, including phage therapy, nanoparticle application, and quorum sensing inhibition [25][26][27][28][29][30][31]. These strategies aim to augment or substitute conventional antibiotic treatments in addressing the rising tide of antibiotic resistance.

2. New Treatment Options

Managing *P. aeruginosa* infections has always been a clinical challenge due to its intrinsic and acquired resistance mechanisms. Traditionally, the primary treatment approach was monotherapy with antipseudomonal agents such as FQ, PIP-TZB, or carbapenems [32][33][34]. However, the emergence of MDR strains has prompted a shift towards combination therapy [35]. Due to their synergistic effects, common combinations include β-lactam agents with aminoglycosides or FQ [36]. Another reason for using combination therapy is to counter the bacteria's ability to form biofilms, which are inherently resistant to many antibiotics. It is also crucial to consider the phenomenon of inducible resistance, where the bacteria can upregulate specific resistance genes in response to certain antibiotics [37]. The different types of resistance mechanisms will be further discussed.

The rise of MDR strains has necessitated the development of new antibiotics. Notable additions to the therapeutic arsenal include TOL-TZB, CAZ-AVI, IMI-REL, and FDC.

TOL-TZB (Zerbaxa®) is a novel antibiotic combination with a next-generation cephalosporin and TZB, a suicidal BLI [38]. This combination has an enhanced affinity for PBPs and potent activity against *P. aeruginosa*, including ESBL and AmpC-producing strains [39]. Clinical studies have emphasized its efficacy against Pseudomonas infections, especially in complicated urinary tract (cUTI) and intra-abdominal infections (cIAI) [40]. Caston et al. treated 20 infections caused by *P. aeruginosa* MDR with TOL-TZB, which included 12 cases of septic shock, 6 cases of pneumonia, 1 case of otomastoiditis, and 1 Central Line-associate Bloodstream Infection (CLABSI), reporting a clinical success rate of 75% [41]. Gallagher et al. treated 205 infections caused by *P. aeruginosa* MDR, primarily pneumonia (59%), and reported a clinical success rate of 74%. Interestingly, they highlighted the importance of the prompt administration of TOL-TZB (within four days), identifying it as a predictor of clinical

success [42]. This observation aligns with previous studies that associated a delay in initiating effective antibacterial therapy with increased mortality in serious bacterial infections, including HAP [43][44].

An observational study involving 200 patients compared the outcomes of a TOL-TZB-based regimen versus polymyxin or aminoglycoside-based therapy [45]. In this study, a favorable clinical outcome was observed in 81% of patients in the TOL-TZB arm versus 61% of patients in the polymyxin- or aminoglycoside-based regimen arm. This difference was statistically significant.

Recently, an ASPECT-NP study involving patients with nosocomial pneumonia caused by Gram-negative pathogens was published. Pneumonia is the most frequent healthcare-associated infection acquired in the Intensive Care Unit (ICU), with high mortality rates [46][47][48]. Hospital-acquired pneumonia (HAP) can be distinguished as ventilator-associated pneumonia (VAP) or hospital-acquired ventilator-requiring pneumonia (vHAP) [49]. Within HAP, vHAP has the highest mortality [46][50].

The ASPECT-NP trial demonstrated the noninferiority of TOL-TZB to MEM for treating vHAP and VAP in both the primary endpoint of 28-day all-cause mortality and the secondary endpoint of clinical cure at the test-of-cure visit, respectively [51]. In the subgroup of vHAP, the ASPECT-NP trial also demonstrated lower mortality in the arm of patients treated with TOL-TZB compared with the arm of patients treated with MEM [51]. This result was further evaluated with multivariable analysis by Kollef et al., confirming the protective effect of TOL-TZB in this special subgroup population [52], although additional studies are needed for confirmation of these findings.

The distinct pharmacological profile of TOL-TZB, marked by enhanced activity against *P. aeruginosa*, makes it a valuable option where resistant Pseudomonas strains are prevalent or suspected [53][54].

CAZ-AVI (Zavicefta®) combines CAZ, a third-generation cephalosporin with potent antipseudomonal activity, and AVI, a non-BL/BLI [55]. AVI effectively neutralizes a broad spectrum of β-lactamases, including carbapenemases like KPC, OXA-48 [56], and GES [49]. Horcajada et al. reported in vitro susceptibility to CAZ-AVI ranging from 66% to 86% for MDR *P. aeruginosa* strains collected from all over the world [57].

In the literature, some studies have highlighted the efficacy of CAZ-AVI in treating various infections due to MDR *P. aeruginosa*, from cUTIs to HAP [58][59][60]. However, clinical trials involving CAZ-AVI treatments are scarce. Stone et al. reported pooled data from five Randomized Controlled Trials (RCTs), showing a favorable clinical outcome in patients treated with CAZ-AVI versus patients treated with more traditional treatment, albeit within the limitations of the study [61].

Nevertheless, the literature concerning the real-world use of CAZ-AVI is spreading. Several studies have been published, underlying positive outcomes in favor of CAZ-AVI in treating MDR *P. aeruginosa* infections [62].

The Infectious Diseases Society of America (IDSA) indicates CAZ-AVI as one of the drugs of choice in the treatment of MDR and difficult-to-treat (DTR)-*P. aeruginosa* strains, both in urinary tract infections and outside urinary tract infections, when tested susceptible [63].

FDC (Fetcroja®) is a siderophore cephalosporin with a unique penetration mechanism. It utilizes the iron-transport mechanism to penetrate bacterial cells, making it active against a broad spectrum of Gram-negative microorganisms, including CRP [64][65]. It is also effective against MBL. Hacket et al. demonstrated in vitro its activity against most MDR *P. aeruginosa* (99.2%), including those resistant to CAZ-AVI and TOL-TZB [66]. Lasarte-Monterrubio et al. evaluated the in vitro activity of FDC (and other novel antibiotic combinations) against strains of *P. aeruginosa* specifically resistant to CAZ-AVI and TOL-TZB [67], showing that FDC was the most active agent.

The SIDERO surveillance program, conducted between 2014 and 2019, showed a susceptibility rate to FDC of CRP strains of 99.8%, according to CLSI breakpoints [68].

The randomized APESK-cUTI demonstrated the non-inferiority of FDC versus IMP-REL in the treatment of complicated urinary tract infections in hospitalized patients for the primary endpoint of composite microbiological eradication and clinical cure at the test-of-cure visit [69].

In the APESK-NP study evaluating the efficacy and safety of FDC for the treatment of nosocomial Gram-negative pneumonia, FDC demonstrated non-inferiority to the MEM treatment. Of all the cases, *P. aeruginosa* represented the second most common pathogen in the FDC arm. Clinical success was achieved in 67% of pneumonia cases caused by *P. aeruginosa*, without statistical difference from the pneumonia cases caused by *P. aeruginosa* in the MEM arm [70].

However, further studies on its efficacy in real life are needed to better assess its effectiveness.

IMP-REL (Recarbrio®) combines IMP, a carbapenem approved in 1985, and REL, a BLI that enhances IMP's activity by protecting it from enzymatic degradation. This combination is active against class A and class C β-lactamases. On the other hand, it is ineffective against OXA-48 and MBLs [71].

The SMART study, a surveillance study conducted in several countries across the world, assessed the susceptibility of IMP-REL [72]. Furthermore, Lob et al. showed that the addition of REL restored the activity of IMP against *P. aeruginosa* strains resistant to IMP alone.

Mushtaq et al. collected *P. aeruginosa* clinical strains producing ESBL and Carbapenemases, showing an 80.5% susceptibility for IMP-REL [73]. In this study, the main mechanism of resistance was the production of beta-lactamases not susceptible to inhibition by REL, such as MBLs, OXAs, and GES.

In the RESTORE-IMI clinical trial, IMP-REL demonstrated greater efficacy than COL/MEM against *P. aeruginosa* infection (81% vs. 63%). However, this difference was not statistically significant due to the small sample size [74].

The RESTORE-IMI 2 clinical trial, a randomized, double-blind controlled trial, was conducted to assess the efficacy of IMP-REL in adult patients with HAP/VAP [75]. IMP-REL was non-inferior to the comparator (PIP-TZB) for both endpoints (day 28 all-cause mortality and favorable clinical response at early follow-up). In this study, *P. aeruginosa* was the second most abundant pathogen isolated.

IDSA guidelines recommend IMP-REL as one of the drugs of choice in the treatment of cUTIs and infections outside the urinary tract due to DTR *P. aeruginosa* strains when tested as susceptible [63].

In addition, promising antibiotics are coming into the pipeline, such as cefepime/enmetazobactam, cefepime/zidebactam, cefepime/taniborbactam, and plazomicine.

These FEP-based antibiotics had broad-spectrum activity against Gram-positive and Gram-negative bacteria. The distinguishing factor is the specific BLI paired with FEP to shield it from enzymatic degradation. While all four inhibitors fall under the category of next-generation BLI, Enmetazobactam is classified as a penicillanic acid sulfone, Taniborbactam as a boronic acid derivative, and Zidebactam as a diazabicyclooctane [76]. Their effectiveness is still being evaluated, but the clinical trials have yielded promising results [77][78][79]. However, no real-life studies compare these three molecules [80]. J Vázquez-Ucha et al. assessed the in vitro efficacy of these molecules, finding that cefepime/zidebactam was the most potent combination against carbapenemase-producing Enterobacterales, followed by cefepime/taniborbactam and cefepime/enmetazobactam. Furthermore, Moya et al. highlighted that zidebactam alone has significant activity against *P. aeruginosa*. This effect is due to the inhibition of PBP2, leading to the creation of spheroplasts, the disruption of the outer membrane, and, as a result, protection against common membrane-bound resistance mechanisms exhibited by *P. aeruginosa* [76].

Plazomicin is a next-generation aminoglycoside antibiotic synthetically derived from sisomicin [81]. It works by inhibiting bacterial protein synthesis, leading to dose-dependent bactericidal activity. One of its significant advantages is its activity against bacterial strains harboring clinically relevant AMEs [82]. However, it is worth noting that plazomicin is not active against bacterial isolates expressing ribosomal methyltransferases, which can lead to aminoglycoside resistance [82]. Focusing on *P. aeruginosa*, plazomicin has shown promising data [83]. The antibiotic demonstrates synergistic activity when combined with other agents like FEP, Doripenem, IMP, or PIP/TZB [84].

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