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Review

Evidence-Based Treatment of *Pseudomonas aeruginosa* Infections: A Critical Reappraisal

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Abstract: Multidrug-resistant (MDR)/extensively drug-resistant (XDR) *Pseudomonas aeruginosa* is emerging as a major threat related to adverse patient outcomes. The goal of this review is to describe evidence-based empiric and targeted treatment regimens that can be exploited when dealing with suspected or confirmed infections due to MDR/XDR *P. aeruginosa*. *P. aeruginosa* has inherent resistance to many drug classes, the capacity to form biofilms, and most importantly, the ability to quickly acquire resistance to ongoing treatments. Based on the presence of risk factors for MDR/XDR infections and local epidemiology, where large proportions of strains are resistant to classic beta-lactams, the recommended empirical treatment for suspected *P. aeruginosa* infections is based on ceftolozane-tazobactam or ceftazidime-avibactam. Where local epidemiology indicates low rates of MDR/XDR and there are no risk factors, a third or fourth generation cephalosporin can be used in the context of a "carbapenem-sparing" strategy. Whenever feasible, antibiotic de-escalation is recommended after antimicrobial susceptibility tests suggest that it is appropriate, and de-escalation is based on different resistance mechanisms. Cefiderocol and imipenem-cilastatin-relebactam withstand most resistance mechanisms and may remain active in cases with resistance to other new antibiotics. Confronting the growing threat of MDR/XDR *P. aeruginosa*, treatment choices should be wise, sparing newer antibiotics when dealing with a suspected/confirmed susceptible *P. aeruginosa* strain and choosing the right option for MDR/XDR *P. aeruginosa* based on specific types and resistance mechanisms.

Keywords: *Pseudomonas aeruginosa*; resistance; treatment; multidrug-resistant bacteria; extensively drug resistant

Citation: Karruli, A.; Catalini, C.; D'Amore, C.; Foglia, F.; Mari, F.; Harxhi, A.; Galdiero, M.; Durante-Mangoni, E. Evidence-Based Treatment of *Pseudomonas aeruginosa* Infections: A Critical Reappraisal. *Antibiotics* **2023**, *12*, 399. https://doi.org/10.3390/antibiotics12020399

Academic Editors: Andrea Marino, Stefano Stracquadanio, Stefania Stefani and Floriana Gona

Received: 22 January 2023
Revised: 11 February 2023
Accepted: 14 February 2023
Published: 16 February 2023

1. Introduction

Pseudomonas aeruginosa is a Gram-negative rod commonly associated with nosocomial infections. In the 2017 global priority list of pathogens, the World Health Organization (WHO) ranked *Pseudomonas aeruginosa* in the category of highest priority [1]. It is also part of the ESKAPE pathogens, a set of six microorganisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) with peculiar features in terms of increasing resistance patterns; indeed, ESKAPE are not only growing in terms of the quantity of resistance, i.e., increasing incidence, but also due to quality because of the development of new resistance mechanisms [2]. *Pseudomonas aeruginosa* was the fifth most common cause of hospital-acquired infections (HAI) in a point prevalence study from 28 European countries in 2016–2017, with a prevalence of

7.1%. In this study, HAI had an overall prevalence of 6.8%, of which 33.1% were attributed to multidrug-resistant (MDR)/extensively drug-resistant (XDR) pathogens [3]. The prevalence *of P. aeruginosa* may be up to 23% in patients with intensive care unit (ICU)-acquired infections [4] and the prevalence of resistant *P. aeruginosa* may reach 48.7% in the ICU [5]. As reported by the U.S. Centers for Disease Control and Prevention (CDC), 32,600 hospitalized patients were infected by MDR *P. aeruginosa* in 2017 [6].

MDR/XDR *P. aeruginosa* has become a major threat related to healthcare with negative consequences in terms of increased mortality, morbidity, and healthcare costs [7–9]. The treatment of these infections remains challenging and requires top skills in the context of antimicrobial stewardship programs.

Accordingly, the goal of this review is to critically reappraise the most recent available evidence in order to describe potential empiric and targeted treatment regimens that can be used for *P. aeruginosa* infections that are suspected or confirmed to be MDR/XDR. We also summarize de-escalation strategies based on antimicrobial susceptibility results and the mechanisms of resistance.

2. Search Strategy and Design of the Review

The authors conducted an extensive literature review by utilizing the MEDLINE/Pubmed and Cochrane library databases and searching for articles regarding *P. aeruginosa* epidemiology, infection syndromes, resistance mechanism, diagnosis, treatment, both empirical and targeted (definitive) regimes, and outcomes. In order to better put into context the data on treatment choices, we also briefly recap the most important microbiological features of *Pseudomonas aeruginosa*. The search terms included a combination of the word *P. aeruginosa*/MDR *P. aeruginosa* in addition to one of the following: "treatment", "risk factors", "biofilm", "new beta lactams", " antimicrobial susceptibility testing", and "resistance mechanisms". While we searched for studies regardless of their language, only studies reported in English were included.

3. *Pseudomonas aeruginosa* Information Path: Walking in the Right Direction

3.1. Resistance Patterns and Infection Syndromes

As per Magiorakos's definition, MDR *Pseudomonas* is defined as being not susceptible to at least one antibiotic in at least three antibiotic classes to which it is usually susceptible, while XDR *Pseudomonas* is defined when there is non-susceptibility to at least one antimicrobial agent in all but two or fewer antimicrobial classes [10]. In 2018, a new concept of "difficult-to-treat resistance" (DTR) was introduced [11]. DTR is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following: ceftazidime, cefepime, piperacillin-tazobactam, imipenem-cilastatin, meropenem, ciprofloxacin, levofloxacin, and aztreonam. According to data published by the European Centre for Disease Prevention and Control (ECDC) in 2020, 30.1% were resistant to at least one antibiotic among carbapenems, fluoroquinolones, ceftazidime, piperacillin-tazobactam, and aminoglycosides, whereas 17.3% were resistant to two or more antibiotics [12].

As observed, 9.4% of the isolates from 29 European countries were resistant to aminoglycosides, 15.5% were resistant to ceftazidime, 17.8% were resistant to carbapenems, 18.8% were resistant to piperacillin-tazobactam, and 19.6% were resistant to fluoroquinolones [12] (Figure 1). Countries with a higher prevalence of *P. aeruginosa* were also those with the highest prevalence of Gram-negative resistance, probably due to shared risk factors.

Usually, the most common infections due to PA are respiratory tract infections, including hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP), urinary tract infections (UTI), bloodstream (BSI), and skin and soft tissue infections. The most common types of *P. aeruginosa* infection are lower respiratory tract infections; it has a prevalence of 10–20% in VAP, which is the second most common pathogen after *S. aureus*. Mortality in VAP and bloodstream infections due to *P. aeruginosa* may be as high as 40% [13] (Figure 2). *P. aeruginosa* is the most common cause of otitis externa and keratitis and is also a common pathogen in diabetic foot infections and endocarditis [14–16].

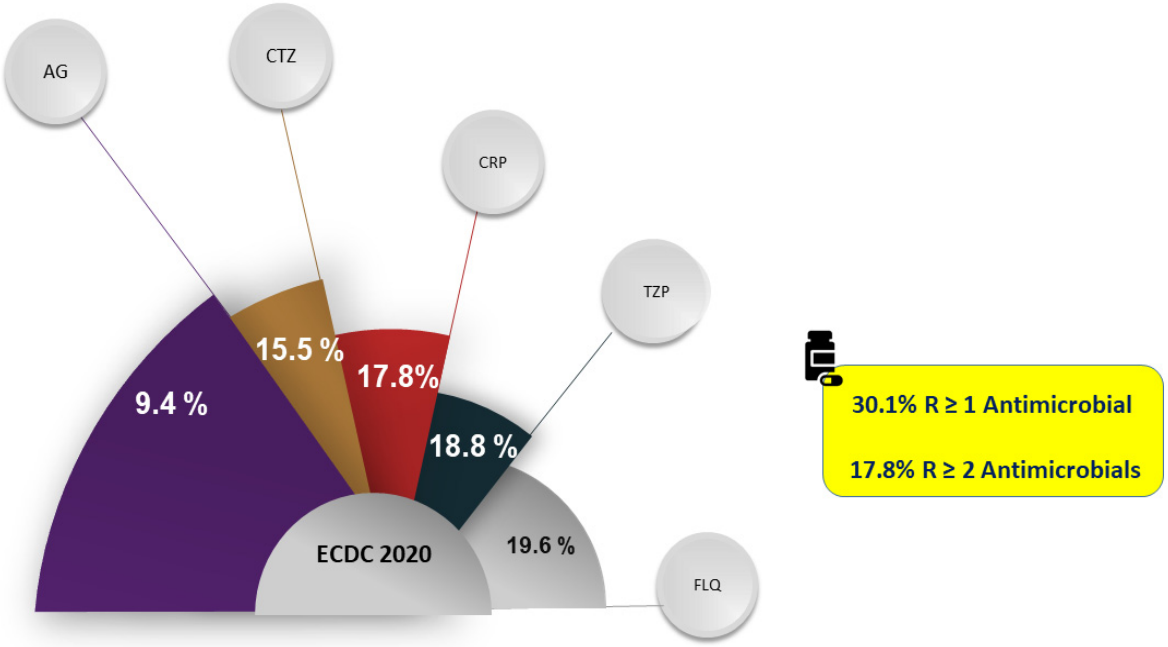

Figure 1. Prevalence of *Pseudomonas aeruginosa* resistance to common antimicrobials/classes in Europe. Abbreviations: AG, aminoglycosides; CTZ, ceftazidime; CRP, carbapenems; FLQ, fluoroquinolones; TZP, piperacillin-tazobactam; R, resistant, ECDC, European Centre for Disease Prevention and Control; R, resistant [12].

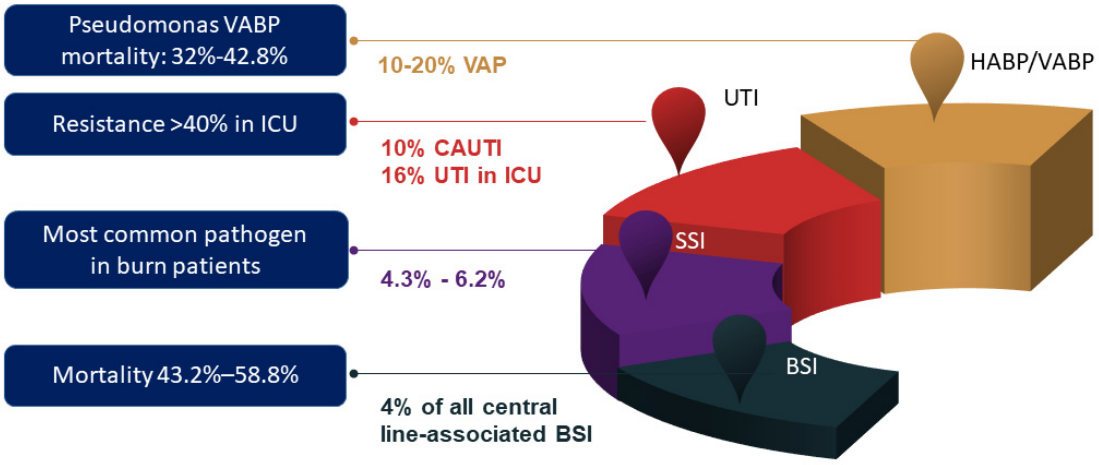

Figure 2. Most common healthcare–associated infections caused by *P. aeruginosa* [13]. Abbreviation: BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; UTI, urinary tract infection; ICU, intensive care unit; HAP, hospital-acquired pneumonia; SSI, surgical site infection, VAP, ventilator-associated pneumonia.

3.2. P. aeruginosa Diagnosis

3.2.1. Planktonic form: Bacterial Identification and Antibiotic Susceptibility Testing

Samples presumptively positive for *P. aeruginosa* are grown and developed on a routine basis from a MacConkey medium; if they exhibit lactose non-fermenting, pale colonies and are oxidase-positive, they can be considered suspects for *P. aeruginosa*. Suspected colonies can be rapidly identified using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF). Antimicrobial susceptibility tests (ASTs) can be performed using disk diffusion (Kirby–Bauer) and broth microdilution (BMD) according to current guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) [17,18]. Moreover, AST can be per-

formed using automated systems, such as Vitek 2, or gradient tests, including E-tests. Typical antibiotics tested are grouped into different categories: β-lactams (ceftazidime, cefepime, piperacillin-tazobactam, and aztreonam); fluoroquinolones (levofloxacin and ciprofloxacin); aminoglycosides (amikacin, gentamicin, and tobramycin); carbapenems (imipenem-cilastatin, meropenem, and doripenem); and colistin [19]. Resistance should be defined as when an isolate is resistant to an antibiotic to which it was previously susceptible. The strains with intermediate susceptibility to antimicrobial agents are now considered susceptible if an elevated exposure to the antibiotic can be attained. Based on the AST results, *P. aeruginosa* should be classified into carbapenem-resistant, fluoroquinolone-resistant, aminoglycoside-resistant, cephalosporin-resistant, and piperacillin/tazobactam-resistant, using the most current standard definitions, or *phenotypes* (Table 1) [20].

Table 1. *Pseudomonas aeruginosa* resistance based of antibiotic classes.

	Individual Antimicrobials Tested against *P. aeruginosa*		
Phenotype	Resistant to at least 1 of the below compounds		
Carbapenem-resistant	Imipenem-cilastatin	Meropenem	Doripenem
Cephalosporin-resistant	Ceftazidime	Cefepime	
Fluoroquinolone-resistant	Ciprofloxacin	Levofloxacin	
Aminoglycoside-resistant	Amikacin	Gentamycin	Tobramycin
Ureido penicillin-resistant	Piperacillin	Piperacillin-Tazobactam	

Regarding new antibiotics, a study on 200 *P. aeruginosa* isolates assessed the efficacy of the Vitek-2 automatic system, disk diffusion, and gradient tests in detecting antibiotic resistance in comparison to the gold standard BMD, and the study showed that ceftazidime/avibactam disk diffusion and gradient tests had a good performance, whereas ceftolozane-tazobactam gradient tests performed better compared to disk diffusion and Vitek-2 [21]. For meropenem-vaborbactam, both Etest and Vitek-2 proved to be accurate [22,23]. BMD remains the gold standard for Cefiderocol as gradient strips are discouraged and many cefiderocol-resistant isolates may fail the diagnosis with disc diffusion [24]. Moreover, AST for colistin, a classic antibiotic used to treat *Pseudomonas* spp. infections, is usually carried out with BMD due to the low accuracy of automated systems and poor diffusion in disk and gradient tests, which underestimate the MIC of colistin, thereby overestimating colistin activity [25,26].

In 2019, a new concept of "intermediate susceptibility" was introduced as being susceptible with increased drug exposure. This means that with the optimization of PK/PD parameters, increased doses, or the optimized mode of antibiotic administration, a microorganism could be considered susceptible to that antibiotic despite the MIC ranging between S and R breakpoints according to EUCAST criteria [27].

Recently, EUCAST has defined new breakpoints for susceptibility according to MIC for *P. aeruginosa.* Most antibiotic classes have an arbitrary breakpoint <= 0.001 mg/L (which is generally lower than the actual MIC of most agents) classifying all these antibiotics as susceptible with increased exposure. In Table 2, we list antipseudomonal antibiotics and current MIC breakpoints according to EUCAST 2023 compared to 2019 EUCAST criteria when the new definition was introduced [28]. The antibiotic classes affected by this change are mostly beta lactams, including ceftazidime, cefepime, piperacillin-tazobactam, aztreonam, imipenem-cilastatin, and fluoroquinolones such as ciprofloxacin and levofloxacin. They are now mostly "susceptible with increased exposure" since their actual MIC in clinical practice is always higher than the susceptibility breakpoint.

Table 2. Antipseudomonal agents and the dynamics of their MIC breakpoint change.

Traditional Antibiotics	EUCAST 2019 * MIC Breakpoints		EUCAST 2023 ** MIC Breakpoints		New Antibiotics	EUCAST 2019 * MIC Breakpoints		EUCAST 2023 ** MIC Breakpoints	
	S≤	R>	S≤	R>		S≤	R>	S≤	R>
Beta Lactams									
Cephalosporin									
Ceftazidime	8	8	0.001	8	Ceftazidime-Avibactam	8	8	8	8
Cefepime	8	8	0.001	8	Ceftolozane-Tazobactam	4	4	4	4
					Cefiderocol			2	2
Ureidopenicillin									
Piperacillin/tazobactam	16	16	0.001	16					
Carbapenem									
Imipenem-cilastatin	4	4	0.001	4	Imipenem-Cilastatin-Relebactam				
Meropenem	2	8	2	2/8	Meropenem-Vaborbactam	8	8	8	8
Doripenem			0.001	2					
Monobactam									
Aztreonam	16	16	0.001	16	Aztreonam-Avibactam				
Other antibiotics									
Polymixin									
Colistin	2	2	4	4					
Fluoroquinolones									
Ciprofloxacin	0.5	0.5	0.001	0.5					
Levofloxacin	1	1	0.001	2					
Aminoglycosides									
Gentamycin	4	4	IE	IE	Plazomicin				
Amikacin	8	16	16	16					
Tobramycin	4	4	2	2					
Fosfomycin									

Abbreviations: EUCAST, European Committee on Antimicrobial Susceptibility Testing; IE, insufficient evidence; S, susceptible; R, resistant. * EUCAST breakpoint when the new intermediate definition was introduced. ** Current EUCAST breakpoints.

Further tests such as molecular and PCR-based methods can be applied in diagnoses to obtain early results, including the identification of the implied pathogens, or to investigate the resistance profiles of specific isolates; this method can be used to detect the presence of specific resistance enzymes such as Ambler class C beta-lactamases (AmpC), *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi Metallo-ß-lactamase (NDM), Verona Integron-encoded Metallo-β-lactamase (VIM), imipenemases (IMP), Guiana extended-spectrum β-lactamase (GES), or oxacillinases (OXAs).

3.2.2. Sessile form: Biofilm Detection

All mentioned methods use the planktonic (free-living) form of *P. aeruginosa* bacteria. Biofilm-forming bacteria have in contrast different resistance characteristics compared to their planktonic counterpart in terms of different architectures of bacterial cooperation, gene expression, and biochemical activity [29]. Biofilm is a never-ending cycle composed of more than one type of bacteria/microbe organized in sessile forms covered by a matrix of extracellular polymeric substances (EPS) [30]. As observed, 90% of the *P. aeruginosa* biofilm is composed of a matrix of polysaccharides, extracellular DNA (eDNA), proteins, and lipids, making an efficient barrier to antibiotic entry [31–33]. Biofilm is known as "the city of microbes" [34], with the matrix being the "house of the biofilm cells" [35]. When bacteria switch to biofilm growth types, sessile forms may undergo major phenotypic changes [36–38], with an increase in the gene expression of efflux pumps, cell wall components, and peptidoglycan synthesis [39,40]. In fact, it was shown that the MIC of different antibiotics within biofilms may increase by 10–1000-fold [41].

Biofilm production is also implicated in multidrug-resistant *P. aeruginosa* (MDR-PA). A study showed that cephalosporins and carbapenems and biofilm-producing *P. aeruginosa* exhibited a 50% susceptibility rate compared to the non-biofilm-producing strains

showing a 100% and 81.8% sensitivity, respectively [42]. Biofilm was shown to affect antimicrobial resistance also in other types of bacteria [43,44]. Various methods can be used to detect biofilm formation in *P. aeruginosa*, with some having a better performance than others [45,46]. Some tests are time-consuming, and omic tools may require qualified technical expertise [47]. However, from tube adherent to microtiter assays, MALDI-TOF and omic analyses are not part of standardized protocols [47,48]. Moreover, currently, the implementation of standardized breakpoint values to assess the MIC of different antibiotics within biofilms remains an unmet need [47].

3.3. Risk Factors for P. aeruginosa/Resistant P. aeruginosa Infection

Risk factors for *P. aeruginosa* infections are burns, open wounds, and post-surgery status for soft tissue infections; urinary catheter for urinary tract infections; immune compromise for bloodstream infections; and old age, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and mechanical ventilation for respiratory infections [49].

For respiratory infections, factors associated with *P. aeruginosa* community-acquired pneumonia (PA-CAP) were prior PA colonization/infection, prior tracheostomy, bronchiectasis, severe COPD, and prior invasive respiratory or vasopressor support (IRVS), while factors associated with MDR-PA CAP were tracheostomy, previous colonization/infection, and IRVS [50]. The longer duration of hospitalization/ICU stay was associated with VAP due to *P. aeruginosa* [51,52].

Regarding resistant isolates, various studies have tried to identify risk factors for MDR *P. aeruginosa* acquisition. A systematic review of 28 articles evidenced that the development of MDR isolates was associated with prior antibiotic use and prior hospitalization or ICU stay [53]. Another systematic review of 22 studies in Asia-Pacific countries evidenced previous exposure to antimicrobials, mechanical ventilation, and previous hospitalization as risk factors for *P. aeruginosa* infections. Risk factors for MDR isolates included mechanical ventilation, previous hospitalization, diabetes mellitus, surgery, prolonged hospital stay, and higher Acute Physiology and Chronic Health Evaluation (APACHE) II score [54].

Other studies identified ICU stay, bedridden state, having high invasive devices scores, being treated with broad-spectrum cephalosporins and with aminoglycosides, mechanical ventilation, higher severity index score, previous hospitalizations, and co-morbidities (diabetes mellitus, renal failure, COPD, and cystic fibrosis) as significant risk factors for MDR *P. aeruginosa* carriage [55–59]. Similar factors were seen also in other resistant Gram-negative infections [60–62]. Moreover, the factors associated with the presence of *P. aeruginosa* infections are broadly similar to those associated with MDR-PA [49,50,63,64] probably due to the nosocomial nature of most PA infection acquisitions [65].

3.4. Major Resistance Mechanisms

P. aeruginosa exerts its resistance by possessing inherent one-to-many drug classes [66,67], the ability to quickly acquire resistance to ongoing treatments, and the capacity to form biofilm [68]. The known mechanisms of PA resistance include intrinsic resistance: outer membrane permeability, overexpression of efflux systems, and antibiotic-inactivating enzymes; acquired resistance: horizontal gene transfer and mutations to genes encoding for efflux pumps, porins, penicillin-binding proteins, and enzymes; and adaptive resistance: continuous antibiotic exposure and overexposure to environmental stress [69].

The mechanisms of action of classic antipseudomonal antibiotics are numerous: bacterial cell wall inhibition for beta-lactam agents such as ceftazidime/cefepime, piperacillin-tazobactam, imipenem-cilastatin, meropenem, doripenem, and aztreonam; blockage of DNA synthesis for fluoroquinolones; and protein synthesis inhibition for aminoglycosides [69]. The major mechanisms of resistance of *P. aeruginosa* are described in Table 3 [66,68–73].

Table 3. Major resistance mechanism of *P. aeruginosa* based on antibiotics classes.

	Resistance Mechanisms			
Antibiotic class	Mechanism 1	Mechanism 2	Mechanism 3	Mechanism 4
Beta-lactams	chromosomal AmpC hyper-expression	OprM porin mutation or loss	OXA-1 & -2 enzyme production	MexXY efflux pump overexpression
Aminoglycosides	altered permeability	cytoplasm expression of aminoglycoside-modifying enzymes, such as aminoglycoside-2″-O-nucleotidyltransfe ANT (ANT 2″Ia) and aminoglycoside 4′-O-adenylyltransferas (ANT 4′-IIb	overexpression of MexXY efflux pumps	
Fluoroquinolones	gyrase (gyr A)—topoisomerase expression; (par C) mutations	altered permeability	efflux systems	
Carbapenems	OprD porin loss	MexXY efflux pump expression	beta-lactamase production	

Multiple mechanisms of resistance often coexist and cooperate to confer *P. aeruginosa* resistance to multiple antimicrobials, thus contributing to challenging treatment efforts [74].

3.5. Treatment

3.5.1. Empirical Treatment

Empirical treatment should be initiated as soon as cultures are collected, as early (and appropriate) therapy is associated with a better prognosis [75] and mostly so in patients with sepsis or septic shock.

Empirical treatment is usually based on the presence of risk factors and local epidemiology for MDR-PA [76,77]. In patients hospitalized in settings where the local epidemiology suggests an MDR-PA rate lower than 25% and without risk factors for MDR-PA, treatment includes one antipseudomonal antibiotic, such as, in decreasing order of priority, carbapenem; piperacillin-tazobactam; cefepime; ceftazidime in cases of BSI, VAP, and SSTI; and all of the above as well as aminoglycosides or colistin in cases of complicated UTI [77]. In patients hospitalized in settings where the local epidemiology suggests an MDR-PA rate higher than 25% and/or the presence of risk factors for MDR-PA/Gram-negative pathogens or in critically ill patients, empirical treatment should include newer beta-lactams ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, or a combination of classic antipseudomonal agents plus an aminoglycoside, colistin, or fosfomycin [77] where new antibiotics are not available.

3.5.2. Combination Therapy or Monotherapy

Regarding combination therapy versus monotherapy, various studies did not demonstrate the superiority of combination therapy compared to monotherapy as a definitive treatment in terms of mortality, microbiological eradication, or resistance development [78–80]. In a study of 1119 patients with bacteremia due to PA, combination treatments did not show lower mortality compared with monotherapy [80]. A systematic review of 69 studies comparing a combination of beta-lactams with aminoglycosides to monotherapy did

not show lower rates of resistance development with combination treatment, and in addition, adverse events such as nephrotoxicity were more common in the combination group [78]. However, in patients with COPD exacerbation, combination therapies with fluoroquinolones proved to be superior in terms of microbiological eradication and mortality [79]. Moreover, when studied in the context of initial empirical treatments, inadequate empirical antibiotic therapy was shown to be associated with increased mortality, whilst adequate combination therapies translated into decreased mortality [81]. Furthermore, one study evidenced that targeted combination treatments with ciprofloxacin correlated with lower rates of mortality compared to monotherapy [82]. The reason for choosing a combination therapy lies in the increased chances that the isolate may be susceptible to at least one of the chosen antibiotics. This applies mostly to classic beta-lactam agents. Regarding new antibiotics, ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam monotherapy is preferred over combination therapy [83]. One option to exploit possible synergistic effects without adding excessive toxicity would be to limit combination therapy, e.g., with an active aminoglycoside, to a short course (maximum 2 to 5 days), with early de-escalation applied to an active monotherapy. Indeed, it was shown that the short course combination of aminoglycosides with beta lactams contributed to synergistic bacterial killing phenomenon at 24 h and lower rates of resistance development probably due to the different mechanisms of action. These antibiotics have no common efflux pump resistance and the cell wall disruption caused by beta lactams may increase the target concentration/penetration of aminoglycosides [84,85] However, this short course combination did not show a reduction in mortality in BSI due to Gram-negative bacteria, including *P. aeruginosa* [86].

In any case, high doses of drugs should always be used, particularly at the outset, and schedules should be adapted to the molecule's pharmacokinetic properties.

3.5.3. Definitive Treatment after AST Results

Once AST results are available, treatment should be individualized/simplified by choosing the most effective antibiotic with the narrowest spectrum of activity. For MDR-PA, a carbapenem or a new beta-lactam agent, where possible with a carbapenem-sparing strategy, should be administered.

Here, we describe the possible scenarios of PA treatments starting from the wild-type PA, which is susceptible to all antipseudomonal antibiotics, to DTR-Pseudomonas, which is resistant to all classical antipseudomonal agents [87,88].

Wild-Type *Pseudomonas aeruginosa*

Despite being the most susceptible form of this microorganism, wild-type *Pseudomonas* has intrinsic resistance to various antibiotics. Its common expression of an inducible AmpC cephalosporinase, usually at low levels, plus efflux systems and low membrane permeability confer the intrinsic resistance of PA to first and second generation cephalosporins, some of the third generation cephalosporins (such as cefotaxime and ceftriaxone), and ertapenem. Interestingly, rather than showing intrinsic resistance to an entire class of antibiotics, PA often shows resistance to individual antibiotics within a given class. As such, the preferable antibiotics in descending order of importance are ceftazidime as first choice (showing the narrowest spectrum of activity compared to cefepime and piperacillin-tazobactam) followed by cefepime and piperacillin-tazobactam. Fluoroquinolones are a valid option in cases when oral treatment can be initiated in an outpatient setting, e.g., in skin and soft tissue infections or in cases of patients that are discharged and need continuing treatment at home after discharge. Carbapenems are the last option used in order to preserve them from more difficult infections. [89,90]. Regarding fluoroquinolones, even though they are the only anti-pseudomonal agents with an oral formulation, they also have important adverse effects in inducing resistance, particularly efflux pump overexpression. Indeed, this mechanism also confers resistance to other antibiotics that may have not been used by that particular patient [91]. Specifically, efflux-system-based resistance is one of the

most important resistance mechanisms of PA, involving a variety of antibiotics including quinolones, aminoglycosides, and beta-lactams such that the use of a single agent may trigger cross-resistance to other agents that are susceptible to that resistance mechanism [77]. As mentioned above, most published studies did not show a superior combination treatment in cases of definitive treatments. However, a question mark remains regarding empirical treatment, where combination treatment increases the chance of using at least one active (and possibly effective) antibiotic. Therefore, in cases of definitive treatments, other antibiotics such as aminoglycosides, colistin, or fosfomycin remain as alternatives to backbone agents (i.e., for cases experiencing side effects of classic antipseudomonal agents or with strains resistant to the latter). A more comprehensive discussion of this point follows.

Specific Antibiotic Class, Possible Applications, and Resistance Scenarios

Aminoglycosides

Amikacin, gentamicin, and tobramycin are the aminoglycosides used for *P. aeruginosa* infections. Regarding resistance, the most common mechanism is via antibiotic inactivation by aminoglycoside-modifying enzymes, resulting in a reduction in the affinity of aminoglycosides for ribosome subunit target 30S, thus blocking their activity [77]. Amikacin is the aminoglycoside that is less susceptible to this mechanism [92]. However, these antibiotics should not be used as a monotherapy in infections outside the urinary tract [82,92]. Apart from i.v formulation, other forms have been shown to be effective, such as inhaled tobramycin, which was shown to be effective in the acute exacerbation of cystic fibrosis [93]. Plazomicin, a novel aminoglycoside agent, does not overcome resistance mechanisms such as altered membrane permeability and other aminoglycoside resistance mechanisms, and its use is limited to *P. aeruginosa* urinary infections [94].

Polymixins

Colistin is a drug mostly used in MDR pathogen infections with activity also against *P. aeruginosa*. It is not a novel antibiotic, however, and its use is problematic due to its side effects, such as the increased risk of nephrotoxicity [95]. The combination of intravenous and nebulized formulations was effective and safe in treating VAP due to Gram-negative pathogens, including *P. aeruginosa* [96]. The additive effects of aerosol administration may be due to its concentrations in the epithelial lining fluid (ELF), since it was shown that the i.v. formulation does not reach an adequate concentration in ELF, whereas the aerosol compound does [97]. The empirical use of colistin in Gram-negative pathogens was not associated with higher chances of survival [98]; moreover, combination treatment with meropenem for carbapenem-resistant Gram negatives was not superior to monotherapy [99–101] or compared to synergizing with rifampicin [102].

Fosfomycin Disodium

Fosfomycin disodium is another old antibiotic with a unique mechanism of bactericidal activity, exerted by the inactivation of enzymes important in bacterial cell wall synthesis. Another unique characteristic of this antibiotic, compared to other anti-pseudomonal agents, is the lack of cross-resistance between fosfomycin and other antibiotics, such as beta lactams and aminoglycosides [103]. It is active against resistant isolates of *P. aeruginosa* due to the low rates of use and non-shared resistance mechanism with other antibiotics [104]. However, caution should be exercised in treating with this drug due to the possibility of the rapid development of antibiotic resistance during treatment after exposure. Fosfomycin was shown to be effective in treating PA as a combination therapy with other antipseudomonal agents in cystic fibrosis patients [105] and also as a combination treatment with carbapenems, exhibiting a synergistic effect with decreasing carbapenem MICs [106]. It was shown to be effective in monotherapy for complicated urinary tract infections compared to piperacillin-tazobactam where all patients with *P. aeruginosa* infection achieved clinical cure [107].

High MIC of Conventional Antipseudomonal Beta Lactams

Some PA isolates may be in vitro susceptible to beta-lactam agents but with an MIC near the breakpoint for conventional beta-lactams. In this case, a treatment solution could be the administration of a high-dose, extended infusion of classic beta lactams in order to reach the exposure needed for the right pharmacokinetic and pharmacodynamic target attainment. Such an effect can be achieved by the prolonged exposure of bacteria to a concentration of antibiotics above the MIC, exploiting in this manner the time-dependent effect of beta-lactam agents [108]. Bauer et al. evaluated 87 respiratory/bloodstream infections treated with either the intermittent or extended infusion of cefepime and found that the group given extended infusions had a lower mortality rate [109]. Moreover, piperacillin-tazobactam-extended infusion exhibited lower mortality rates and a shorter hospitalization length, translating into lower healthcare costs as well [110]. However, this treatment strategy needs to be wisely chosen due to difficulties in implementation, such as limiting patient mobility due to prolonged i.v. line infusion and protracted indwelling access of intravenous lines leading to possible infective or thrombotic complications.

Resistance to Carbapenems with Maintained Susceptibility to Cephalosporins

This is a scenario mostly observed in cases with a low expression/limited production of porins (especially OprD). In these cases, isolates are resistant to carbapenems (meropenem and imipenem-cilastatin) due to porin channels being an important mechanism in the bacterial entry for carbapenems. However, the isolate may maintain susceptibility to cephalosporins. Therefore, two treatment options may be applicable: i) new beta lactams (ceftolozane-tazobactam and ceftazidime-avibactam) and (ii) the high-dose extended-infusion of classic "unprotected" cephalosporins. The decision is up to the treating clinician; however, IDSA recommends—after AST repetition and confirmation of the results—starting treatments with conventional cephalosporins in order to preserve newer antibiotics for future infections. In cases with a severe infection and in critically ill patients, the use of new beta lactams could be a more reasonable option [89].

Beta Lactam Resistance

Most common resistance mechanisms found in *P. aeruginosa* include the production of beta-lactamases, such as some ESBL but mostly the hyper-expression of AmpC, which confers resistance to ceftazidime/cefepime, piperacillin-tazobactam, and aztreonam. In this case, carbapenems remain active; thus, the treatment choice is between carbapenems and newer beta lactams.

Carbapenem Resistance

The most common mechanism is the production of carbapenemases, particularly class A KPC or GES and metallo-beta-lactamases such as VIM, IMP, SBL, and other less common ones such as GIM, NDM, and FIM. VIM and IMP have a few variants implicated in *P. aeruginosa* resistance, whereas only one type is identified for others [111]. Metallo-beta-lactamases confer resistance to all antibiotics (including ceftolozane-tazobactam and ceftazidime-avibactam) except aztreonam. In contrast, cefiderocol is not affected [112,113]. Usually, isolates with metallo-beta-lactamase production also express AmpC. The combination of aztreonam/avibactam is therefore a promising option in such resistance settings, as aztreonam is not affected by the hydrolysis of metallo-beta-lactamases, while avibactam inhibits most other co-expressed beta-lactamases, including AmpC [114].

Isolates producing KPC (not a very common resistance mechanism in *P. aeruginosa*) are susceptible to cefiderocol and imipenem-cilastatin-relebactam. Another treatment option for carbapenemase-producing strains could be the combination of aminoglycosides, colistin, or fosfomycin with another antibiotic that is found active in vitro.

DTR *Pseudomonas aeruginosa*

Efflux systems and decreased membrane permeability are the mechanisms of resistance that confer reduced susceptibility to a wide range of anti-pseudomonal antibiotics. Indeed, efflux systems affect beta-lactams, carbapenems, fluoroquinolones, and aminoglycosides,

and decreased membrane permeability mostly affects beta-lactams, fluoroquinolones, and aminoglycosides. Sometimes, different mechanisms cooperate in the same isolate—for example, the modification of OprD mostly affects imipenem-cilastatin (and to a lesser extent meropenem) but does not affect other beta-lactams. However, this mechanism is often associated with other resistance mechanisms such as efflux systems, the hyperproduction of AmpC enzymes, and the mutation of penicillin-binding proteins, making the isolate resistant to most/all conventional anti-pseudomonal antibiotics [76]. In this case, the needed therapeutic approach might be that of a DTR *P. aeruginosa.*

The concept of "difficult-to-treat resistant" (DTR) *Pseudomonas aeruginosa*, proposed in 2018, is based on the not so rare instance of a strain resistant to all of the following antibiotics: ceftazidime, cefepime, piperacillin-tazobactam, aztreonam, imipenem-cilastatin, meropenem, ciprofloxacin, and levofloxacin. IDSA divides the therapeutic approach for DTR-PA into two distinct scenarios: urinary tract infections and non-urinary tract infections. In urinary tract infections, recommended treatment choices are newer beta lactams (ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, and cefiderocol) as the first choice, followed by a single dose of aminoglycosides as a second choice; in complicated and non-complicated infections, the first and second choices are the same, with complicated infections requiring the addition of colistin as an alternative therapy. In infections outside of the urinary tract, the first choices are ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, and as alternative therapy, cefiderocol [89]. Regarding newer beta lactams, there are no available clinical trial data comparing the efficacy and safety of newer beta lactams with each other in/outside of urinary tract infections. Therefore, IDSA does not recommend one new beta lactam over the other; however, they recommend cefiderocol as an alternative treatment in infections outside of the urinary tract due to lack of improvement in the outcome as observed in other new beta lactams (despite performing as well as past backbone treatments for DTR-*P. aeruginosa*) [89]. Another important issue is whether it is rational to use new antibiotics in empirical therapy (being selected for use in cases with local epidemiology positive for resistance to traditional antipseudomonal agents/risk factor for MDR/XDR infections) or as a definitive treatment (being chosen after AST results confirming resistance to other antibiotics and susceptibility to the selected new beta lactam).

New Antibiotics

Ceftolozane-tazobactam, a beta-lactam/beta-lactamase inhibitor, is a relatively novel antibiotic showing efficacy in treating *Pseudomonas* infections (urinary tract, intra-abdominal, and pulmonary infections at double doses) (Aspect trials) [115–117]. It is less affected by efflux systems and decreased membrane permeability [118]. It has a low affinity for hydrolysis by AmpC, but it is affected by carbapenemases [119], and cases with in vivo resistance have been reported with the main mechanism of action being hyper-expression or the modification of intrinsic AmpC and horizontally acquired beta-lactamases [120]. Even though cases with resistance to ceftolozane-tazobactam have been reported, *P. aeruginosa* isolates are usually susceptible to this drug [121].

Ceftazidime-avibactam is a beta-lactam/non-beta-lactam beta-lactamase inhibitor that is not active against metallo-beta-lactamases, and it is affected more by efflux systems and porine changes compared to ceftolozane-tazobactam. Avibactam inhibits the beta-lactamases of class A, KPC, AmpC, and OXA-48. Resistance to KPC was evidenced [108,119], and avibactam is in vitro active also against GES enzymes [108]. The ERACE-PA global study group showed susceptibility to ceftazidime-avibactam of 91% and 72% for carbapenem-susceptible and carbapenem-resistant strains, respectively [121].

Meropenem-vaborbactam is a carbapenem/non-beta-lactam beta-lactamase inhibitor combination showing activities similar to simple meropenem in *P. aeruginosa* infections, as meropenem resistance in *P. aeruginosa* is mostly a result of mechanisms not impacted by vaborbactam. Indeed, vaborbactam inhibits the beta-lactamases of class A and C, while the resistance of *P. aeruginosa* to meropenem is mostly due to efflux systems, reduced membrane permeability, and the beta-lactamases of class B or D [119].

Imipenem-cilastatin-relebactam is another new carbapenem/non-beta-lactam beta-lactamase inhibitor combination. It inhibits the beta lactamases of class A and C but is not active against metallo-beta-lactamases [119]. It was shown to be active for isolates resistant to ceftolozane-tazobactam and ceftazidime-avibactam, making it a valuable option as a rescue therapy [108].

Cefiderocol is a novel siderophore cephalosporin that binds to penicillin-binding proteins, thus preventing the synthesis of the bacterial cell wall. It exploits bacterial iron transporters in order to enter the outer cell membrane. It is poorly affected by efflux systems and porin channel modifications and remains stable against AmpC and metallo-beta-lactamases [119]. Cefiderocol was found to be active against isolates that are resistant to all other newer beta lactams, and it exhibited similar microbiological and clinical efficacy compared to the best available therapy in treating infections due to carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR) [113,122,123].

A synoptic flow chart of empirical and targeted treatment for *P. aeruginosa* infections is presented in Figure 3.

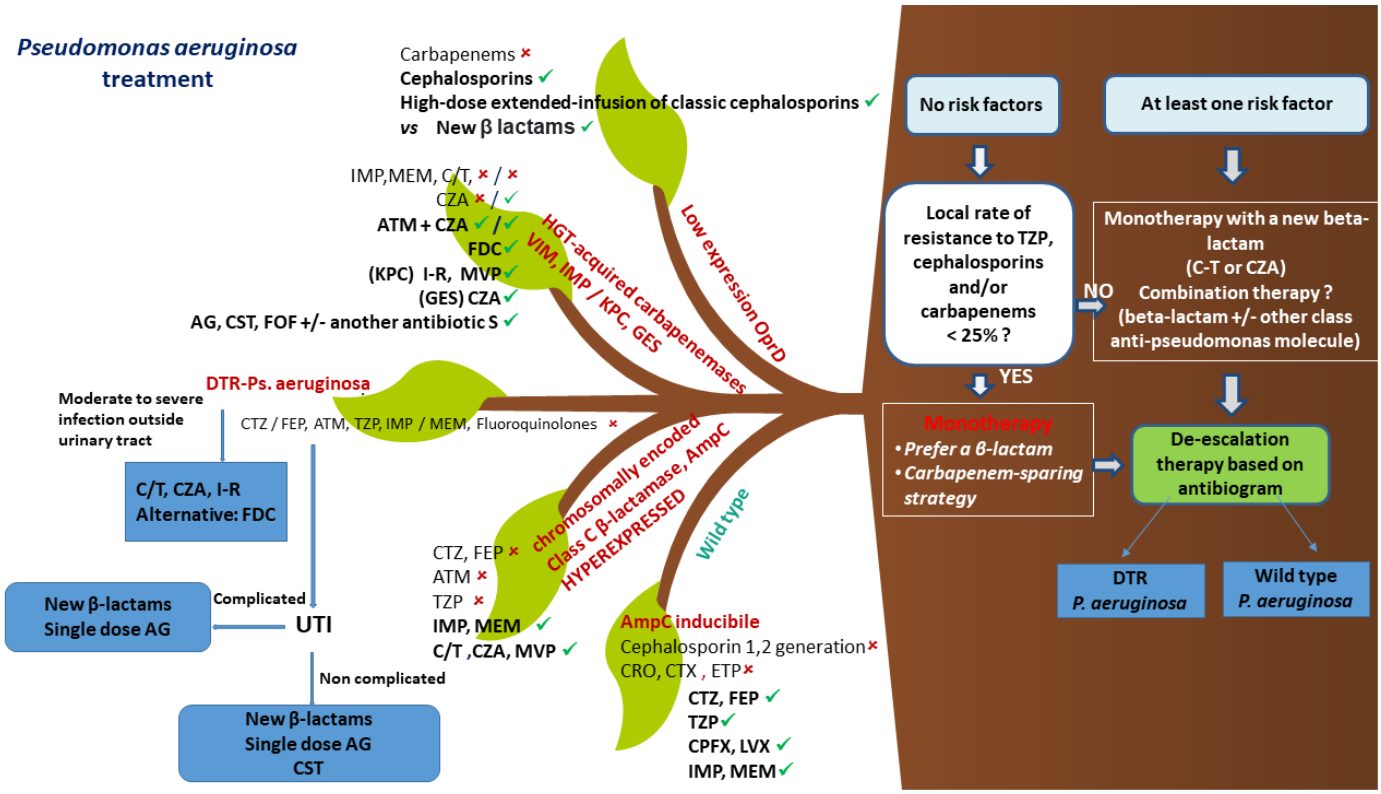

Figure 3. Algorithm for the empirical and targeted treatment of *P. aeruginosa* infections. Abbreviations: AmpC, Ambler class C beta-lactamase; VIM, Verona Integron-encoded Metallo-β-lactamase; IMP, active on imipenem; KPC, Klebsiella pneumonia carbapenemase; GES, Guiana Extended-Spectrum β-lactamase; UTI, urinary tract infections; DTR, difficult to treat resistance; CRO, ceftriaxone; CTX, cefotaxime; ETP, ertapenem; CTZ, ceftazidime; FEP, cefepime; TZP, piperacillin-tazobactam; CPFX, ciprofloxacin; LVX, levofloxacin; IMP, imipenem-cilastatin; MEM, meropenem; ATM, aztreonam; C/T, ceftolozane-tazobactam; CZA, ceftazidime-avibactam; MVP, meropenem-vaborbactam, I-R, imipenem-cilastatin-relebactam; FDC, Cefiderocol; AG, aminoglycosides; CST, colistin; FOF, fosfomycin; OprD, outer membrane porin D; ✓, susceptible; ×, resistant.

4. Conclusions

MDR/XDR *P. aeruginosa* is emerging as a major threat related to adverse healthcare consequences. The importance of infection prevention takes on a particular value because it can rapidly develop resistance even to the newest drugs. Moreover, treatment choices should be cautious, sparing newer antibiotics when dealing with a suspected/confirmed sensitive *P. aeruginosa* and choosing the right option for MDR/XDR cases based on specific types and resistance mechanisms. The use of new antibiotics should be rational, both empirically (being selected for use in cases with local epidemiology positive for resistance to traditional antipseudomonal agents/risk factor for MDR/XDR infections) or as definitive treatments (being chosen after AST results confirming resistance to other antibiotics and susceptibility to the selected new beta lactam). Regarding resistance mechanisms, ceftolozane-tazobactam currently shows less vulnerability to common resistance mechanisms, such as efflux systems and reduced membrane permeability, compared to ceftazidime-avibactam. Imipenem-cilastatin-relebactam and cefiderocol are also unaffected by such mechanisms, and studies evidenced that isolates resistant to ceftazidime-avibactam and ceftolozane-tazobactam may remain susceptible to imipenem-cilastatin-relebactam or cefiderocol. Therefore, it is advisable to preserve the use of these two antibiotics in order to exploit them in cases of absolute need.

Author Contributions: A.K. worked on the concept of the study, performed the literature review, drafted the manuscript, and critically revised the work. C.C. performed the literature revision and critically revised the work. C.D. performed the literature review and critically revised the work. F.F. performed the literature review and critically revised the work. F.M. performed the literature review and critically revised the work. M.G. critically revised the work. A.H. critically revised the work. E.D.-M. worked on the concept of the study, drafted the manuscript, and critically revised the work. All authors have read and agreed to the published version of the manuscript.

Funding: Funded in part by the NIH-sponsored OVERCOME study project to EDM.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The information collected for this study is available upon request to the corresponding Author.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; literature revision; in the writing of the manuscript; or in the decision to publish the results. EDM reports research funding for his Institution from MSD, Pfizer, Angelini, Infectopharm, Advanz pharma, and personal fees or fees to participate in advisory boards or speaker's honoraria from Roche, Genentech, Pfizer, MSD, Angelini, Advanz pharma, Bio-Merieux, Shionogi, Menarini, Abbvie, Sanofi-Aventis, Medtronic, Trx, and DiaSorin.

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