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Antimicrobial treatment of *Pseudomonas aeruginosa* severe sepsis

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Introduction

Pseudomonas aeruginosa (P. aeruginosa) is a major cause of nosocomial infections, particularly bloodstream and respiratory infections, with a high mortality rate of up to 30%[1]. It has intrinsic resistance to many antimicrobials and can quickly develop resistance to most available antibiotics[2]. With the spread of highly resistant strains, the risk of inappropriate empiric treatment is increasing, and has been correlated with increased mortality, especially in severe infections like sepsis[3]. Difficult to treat (DTR) P. *aeruginosa* is a recent definition that indicates resistance to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin and quinolones, and is used in most current guidelines[4].

Empirical Antimicrobial Treatment (EAT)

EAT in severe sepsis should be chosen according to the patient's allergies, comorbidities, primary site of infection, prior antibiotic exposure, and most importantly, local susceptibility patterns.

Combination therapy for *P. aeruginosa* sepsis may decrease the risk of inadequate EAT by combining mechanisms of action. However, the evidence regarding the efficacy of combination EAT is conflicting. While one Cochrane review comparing beta lactam monotherapy and combination with an aminoglycoside (AG) showed similar mortality for patients with *P. aeruginosa* sepsis, another recent meta-analysis evaluating all-cause mortality showed improved survival with combination EAT[5,6].

Given the rise of antimicrobial resistance (AMR), combination EAT should be highly considered in cases of severe sepsis to avoid inappropriate EAT[7]. Two different mechanisms of action should be combined, typically a backbone beta-lactam and a fluoroquinolone (FQ) or preferably, an AG. Prompt de-escalation to monotherapy with a narrower spectrum is highly advised once susceptibility results are available and source control is achieved.

Targeted therapy for *P. aeruginosa* sepsis

P. aeruginosa sensitive to first line agents

First-line beta-lactam agents for *P. aeruginosa* coverage include beta-lactam / beta-lactamase-inhibitor combinations (BL/BLI) (piperacillin-tazobactam and ticarcillin-clavulanate), antipseudomonal cephalosporins (ceftazidime, cefepime and cefoperazone) and antipseudomonal carbapenems (doripenem, meropenem, imipenem). If possible, cephalosporins should be favoured over carbapenems for their higher potency, narrower spectrum, and lower tendency to induce resistance[8].

Antipseudomonal AG (gentamicin, tobramycin, amikacin) should only be used in combination therapy except for urinary tract infections (UTIs)[9]. Levofloxacin and ciprofloxacin are currently the only available oral treatment options for *P. aeruginosa* and should be spared for oral transitioning. Emergence of resistance is possible and should be highly suspected in patients who worsen despite appropriate therapy[8].

P. aeruginosa resistant to first line therapy

P. aeruginosa may acquire resistance to carbapenems through various mechanisms such as production of a carbapenemase, outer membrane protein modification or efflux pumps (**Table**). The potential of co-resistance to multiple first-line agents, especially, between ceftazidime, piperacillin-tazobactam and meropenem is high. In those cases, escalation to second-line agents will likely improve outcomes[10]. Second-line agents include novel BL-BLI like ceftolozane-tazobactam (C/T), ceftazidime / avibactam (CAZ/AVI) and imipenem-cilastatin/relebactam (IMI/REL) or the siderophore cephalosporin, cefiderocol[2].

	C/T	CAZ/AVI	IMP/REL	Cefiderocol	Plazomicin	Fosfomycin	Colistin
Carbapenemase							
Class A (KPC)	No	Yes	Yes	Yes	Yes	Yes	Yes
Class B (MBL)	No	No	No	Yes	Variable	Yes	Yes
Class D (OXA)	No	Yes	No	Yes	Yes	Yes	Yes
OprD	Yes	Yes	Yes	Yes			
MexAB	Yes	No	Yes	Yes			
MexXY	Yes	No	Yes	Yes			

Table 1. Treatment options for Carbapenem-resistant *P. aeruginosa* according to mechanism of resistance. C/T, Ceftolozane-Tazobactam; CAZ/AVI, Ceftazidime-avibactam; IMP/REL, Imipenem-cilastatin-relebactam

C/T has a high affinity to all penicillin-binding proteins (PBP) of *P. aeruginosa* and has been approved for complicated intra-abdominal infections (cIAI), UTIs, and hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Favourable outcomes have been reported in clinical trials comparing C/T to other agents for *P. aeruginosa* HAP including VAP, cIAI, and UTIs. CAZ/AVI has also been approved by the FDA and EMA for the treatment of UTIs, cIAI and infections with resistant Gram-negative pathogens. C/T and CAZ/AVI have been considered key therapeutic agents and have greatly improved outcomes in patients

with *DTR P. aeruginosa*. However, resistance to them has started emerging[11].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggest treatment with C/T as the single first choice for severe DTR pseudomonal infections like severe sepsis[12]. IDSA recommends treatment with either C/T, CAZ/AVI, or imipenem/relebactam for DTR *P. aeruginosa* infections outside the urinary tract[4]. Although C/T is favoured over CAZ/AVI for *P. aeruginosa*, susceptibility to both agents should be obtained as there are C/T-resistant CAZ/AVI-susceptible strains[13]. Real world evidence has confirmed the efficacy of both[1].

Cefiderocol is recommended as an alternative to novel BL/BLI by IDSA. Although there is concern about higher mortality due to the CREDIBLE-CR trial's results, the number of patients with *P. aeruginosa* in that trial was small, hence, these findings may not be generalisable[14]. Cefiderocol remains an option, especially given its activity against metallo-beta lactamases (MBL).

The emergence of MBL-producing *P. aeruginosa* is of significant concern. Aztreonam may resist hydrolysis by MBLs making it an attractive agent in combination with CAZ/AVI[15].

Although many guidelines recommend against the use of polymyxins they might be the only option for the treatment of DTR strains in low resource settings. Although intravenous Fosfomycin may be active against DTR *P. aeruginosa,* monotherapy is only indicated for cases of uncomplicated UTIs due to the risk of emergence of resistance[16].

A single agent, preferably a beta-lactam, should be chosen for DTR isolates since definitive combination therapy has not been shown to improve outcomes and may increase costs and adverse events[1].

Important key elements of therapy

The pharmacokinetics of most antimicrobials are altered following the hemodynamic changes of severe sepsis. Critically ill patients may require dose adjustments. For C/T, higher doses (3g every 8 hours) are recommended in critically ill patients to maintain bactericidal serum concentration[17].

Extended infusion (EI) of beta lactams may help achieve a more sustainable serum concentration and decrease the length of stay[18]. It is also recommended by IDSA and ESCMID for the treatment of non-susceptible strains[4].

The duration of treatment should consider the primary site of infection, the patient's underlying comorbidities, source control, susceptibility results, inflammatory biomarkers, and clinical response. Two to three weeks is currently recommended especially for immunocompromised patients and patients with pneumonia who are at risk of recurrence with shorter regimens[19].

Conclusion

The burden of *P. aeruginosa* severe sepsis is worsened by resistant strains. Novel treatment options have improved patients' outcomes and spared the adverse events of older toxic drugs like polymyxins. Combination empiric therapy should be initiated in critically ill patients to avoid inappropriate antimicrobial therapy and prompt de-escalation when susceptibility results are available.

References

1. Zakhour J *et al*. Antimicrobial Treatment of *Pseudomonas aeruginosa* Severe Sepsis. *Antibiotics (Basel)*. 2022;11:1432
2. Ibrahim D *et al*. Current choices of antibiotic treatment for *Pseudomonas aeruginosa* infections. *Curr Opin Infect Dis*. 2020;33:464–73
3. Albasanz-Puig A *et al*. Effect of Combination Antibiotic Empirical Therapy on Mortality in Neutropenic Cancer Patients with *Pseudomonas aeruginosa* Pneumonia. *Microorganisms*. 2022;10:733
4. Tamma PD *et al*. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. IDSA 2022; Version 1.1 [Accessed Jul 31 2022]
5. Fiore M *et al*. Ceftolozane-Tazobactam Combination Therapy Compared to Ceftolozane-Tazobactam Monotherapy for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis. *Antibiotics (Basel).*2021;10:79
6. Paul M *et al*. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2014;CD003344
7. Rhodes A *et al*. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med.* 2017;45:486–552
8. Carmeli Y *et al*. Emergence of antibiotic-resistant *Pseudomonas aeruginosa:* comparison of risks associated with different antipseudomonal agents. *Antimicrob Agents Chemother*. 1999;43:1379–82
9. Phe K *et al*. Outcomes of empiric aminoglycoside monotherapy for *Pseudomonas aeruginosa* bacteremia. *Diagn Microbiol Infect Dis*. 2019;93:346–8
10. Moise PA *et al*. Collective assessment of antimicrobial susceptibility among the most common Gram-negative respiratory pathogens driving therapy in the ICU. *JAC-Antimicrob Resist*. 2021;3:dlaa129
11. Tamma PD *et al*. Modifiable Risk Factors for the Emergence of Ceftolozane-tazobactam Resistance. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021;73:e4599–606
12. Paul M *et al*. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect*. 2022;28:521–47
13. Teo JQM *et al*. Ceftolozane/Tazobactam Resistance and Mechanisms in Carbapenem-Nonsusceptible *Pseudomonas aeruginosa*. *mSphere*. 2021;6:e01026-20
14. Bassetti M *et al*. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21:226–40
15. Lee M *et al*. Activity of aztreonam in combination with ceftazidime-avibactam against serine- and metallo-β-lactamase-producing *Pseudomonas aeruginosa*. *Diagn Microbiol Infect Dis*. 2021;99:115227
16. Al Salman J *et al*. Management of infections caused by WHO critical priority Gram-negative pathogens in Arab countries of the Middle East: a consensus paper. *Int J Antimicrob Agents*. 2020;56:106104
17. Ruiz J *et al*. Ceftolozane/Tazobactam Dosing Requirements Against *Pseudomonas aeruginosa* Bacteremia. *Dose-Response Publ Int Hormesis Soc*. 2020;18:1559325819885790
18. Thabit AK *et al*. The pharmacodynamics of prolonged infusion b-lactams for the treatment of *Pseudomonas aeruginosa* infections: a systematic review. *Clin Ther*. 2019;41:2397-2415.e8
19. Pugh R *et al*. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev*. 2015;CD007577