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Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*

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ABSTRACT

Pseudomonas aeruginosa is characterized by an important intrinsic resistance to antibiotics and it possess an extraordinary ability to develop resistance to nearly all available antimicrobials through selection of mutations. We review some of the pharmacodynamic principles of antibiotics predicting efficacy, clinical experience with monotherapy and combination therapy, and principles for antibiotic treatment for empirical and directed treatment of *P. aeruginosa* invasive infections.

Key words: ***Pseudomonas aeruginosa*, treatment**

PRINCIPLES FOR THE TREATMENT OF INFECTIONS CAUSED BY *P. AERUGINOSA*

Principles guiding election of antibiotic treatment, whether empirical or directed treatment, in case of suspected or confirmed *Pseudomonas aeruginosa* infections, are those also applying to any severe infection, but with some peculiarities as follows:

1) MIC of main antibiotics active against *P. aeruginosa*. The breakpoint used to categorize *P. aeruginosa* as resistant to one β-lactam or aminoglycoside is from 2-times (piperacillin-tazobactam, imipenem, tobramycin, gentamicin) to 8-times (ceftazidime, cefepime) higher than the one used to consider resistant an enterobacteria. Against most clinical isolates of *P. aeruginosa* susceptible to β-lactams, the MIC of an antibiotic is usually at or close to its breakpoint value (2- 8 mg/L). For this reason, high doses of β-lactams are recommended, even if the strain has been categorized as susceptible in *in vitro* susceptibility tests.

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For the treatment of severe or high bacterial load infections, produced by microorganisms exhibiting MIC ≥4 mg/L of the β-lactam, only elevated doses administered by continuous or extended infusion reach free antibiotic concentrations exceeding 4-times the MIC [1].

In most clinical studies [2] but not in all [3]), continuous or extended infusion of piperacillin-tazobactam, cefepime, ceftazidime or meropenem, for the treatment of infections by Gram-negative bacilli (including *P. aeruginosa*) was more efficacious than intermittent administration with respect to the one or more following parameters: clinical cure rate, microbiological eradication, days with fever, length of ICU or hospital stay and decrease in severity (measured by APACHE II) and/or mortality.

The main determinant for clinical response to an aminoglycoside treatment is the Cmax/MIC value [4]. For the reasons exposed below, the greatest efficacy for a treatment is obtained when Cmax/MIC ≥10. For a MIC value for *P. aeruginosa* of 2-4 mg/L of tobramycin and gentamicin, the recommended Cmax is 30-40 mg/L and for amikacin MIC of 8 mg/L, Cmax should be between 60 and 80 mg/L [5]. Usually these values are not achieved with standard doses.

2) Importance of the bacterial load in the infectious foci. In *P. aeruginosa* infectious foci as pneumonia, purulent tracheobronchitis in the intubated patient, secondary peritonitis, neutropenic colitis and skin and soft tissue infections, the bacterial load at antibiotic treatment initiation is usually high (≥10^7-10^8 CFU).

The ability of granulocytes to eradicate microorganisms is saturable [6]. In rat models of pneumonia by *P. aeruginosa*, when the bacterial load was close to or higher than 2.5 x 10^6 CFU/g of tissue, the bacteriolytic ability of granulocytes was surpassed and bacterial growth occurred [7]. The authors of these studies suggested that in infections with high bacterial load, as VAP, an early and rapid ≥2 log10 CFU/mL decrease

produced by the antibiotic treatment might decrease bacterial density below the cut-off level of granulocyte activity saturation, allowing an optimal contribution for microorganism eradication.

Another important consequence of the presence of a high bacterial load is the increased risk of selection of resistant mutants.

3) Mutation ability and development of resistance in *P. aeruginosa*. Frequency of emergence of resistant mutants within *P. aeruginosa* populations ranges from 10^6 to 10^8 depending on the antibiotic [8]. In the presence of agents damaging DNA (fluoroquinolones) and in biofilm-embedded bacterial growth, the basal rate of emergence of resistant mutants can be around 100 times increased [9].

A bacterial density ≥ 10^7 -10^8 CFU at treatment initiation involves high risk of selection and amplification of the resistant subpopulation under the selective antibiotic pressure. Measures to counter this risk include: a) reduction of the bacterial load through the control of the infectious foci (drainage, debridement, de-obstruction or removal of catheter or infected foreign body), b) initiation of treatment with associations of antibiotics not sharing the main resistance mechanism [10], and c) use of doses and/or routes of administration able to generate an antibiotic concentration higher than MIC for potential resistant mutants in the infectious foci.

Antibiotics (aminoglycoside, ciprofloxacin or levofloxacin) associated with the β-lactam during the first 48-72 h, among other purposes to avoid selection of resistant mutants, should be administered at doses achieving concentrations over the corresponding mutant prevention concentrations (MPCs). Although MPCs are unknown and could not be predicted from MIC values, generally for these antibiotics they are from 8 to 12 times higher than the MIC.

At the 2nd-3rd day of treatment, when deescalation to monotherapy is considered, most patients remain colonized by *P. aeruginosa* in mucosa and bronchial secretion (in case of pneumonia, tracheal intubation or previous bronchial pathology), especially if no inhaled antibiotic treatment with tobramycin, colistin or aztreonam had been administered. Persistence of bronchial colonization does not justify by itself prolongation of IV administration of the aminoglycoside more than 3-5 days.

4) Importance of an appropriate empirical treatment. Studies performed in patients with VAP [11] or bacteremia [12] caused by *P. aeruginosa* showed high mortality rates if the initial empirical antibiotic treatment is not appropriate. Early administration of an appropriate antibiotic treatment has special relevance when the infection presents clinical or biological severity criteria, the patient suffers important immunodepression or comorbidities or has advanced age [13]. Treatment initiation with a β-lactam associated with amikacin, ciprofloxacin or colistin (chosen based on local resistance rates) increases the probability of the appropriateness of the initial empirical schedule [11].

5) Value of antibiotic associations. Usually, the association of a β-lactam and an aminoglycoside shows *in vitro* synergistic activity. However, in clinical practice, the potential synergy of the association does not seem to turn into a tangible improvement of prognosis estimated as survival rate. Most studies carried out in patients with bacteremia [12] or VAP [11] by *P. aeruginosa*, as well as several meta-analyses [14], did not found significant differences in mortality rates between patients receiving β-lactam monotherapy and those receiving a β-lactam and aminoglycoside association. Nevertheless, there are several aspects raising doubts with respect to the strength of these results. Most studies were retrospective analyses, treatments were not randomized, the most severe patients tended to be treated with antibiotic associations [15] and analyses were not adjusted by possible confounding factors. In a significant number of patients, the origin of bacteremia was an urinary tract infection or venous catheter removal, thus, non-severe infections and low bacterial load. In addition, in the aminoglycoside arm nephrotoxicity masking the benefits of the association could not be ruled out since renal failure is an important prognostic factor in critically ill patients. On the other hand, in other studies, a favorable effect of the association versus monotherapy has been reported in the treatment of bacteremia caused by *P. aeruginosa* [16], particularly in neutropenic patients [17], in cystic fibrosis exacerbations [18] and in a meta-analysis of studies on bacteremia by Gram-negative bacilli. However, these results are neither conclusive because in the monotherapy arm patients treated with aminoglycosides were often included [19].

In most clinical situations, the treatment of choice for a β-lactam susceptible *P. aeruginosa* infection is β-lactam monotherapy except in the following cases: 1) during the first 72 hours if the infection presents criteria of severe sepsis or septic shock, 2) in the neutropenic patient, and 3) in nervous central system (meningitis, abscess) or endovascular (endocarditis) infections. Use of associations including a β-lactam should be considered even for the treatment of infections caused by β-lactam resistant pathogens, especially if the resistance level is moderate (MIC 2-4 times higher than the breakpoint value). In this situation, the potential synergy with the second antibiotic could revert β-lactam non-susceptibility, if succeed in lowering the MIC below the resistance level.

6) Clinical efficacy of different antibiotics as monotherapy. Clinical experience evidences that monotherapy with β-lactams shows higher efficacy and/or lower toxicity than monotherapy with aminoglycosides [12] or colistin [20] and similar to monotherapy with a fluoroquinolone (ciprofloxacin) [21] in the treatment of Gram-negative infections, including those by *P. aeruginosa*. However, in some infection sites, as in external malignant otitis, prostatitis, or cystic fibrosis bronchial infections, the use of ciprofloxacin may have advantages over a β-lactam, based on the possibility of oral administration, better penetration in the infectious foci and the probable greater activity in biofilms.

7) Measures to increase antibiotic concentrations in the infectious foci. As mentioned in points 1 and 2, to optimize the PK/PD index and to avoid selection/amplification of resistant subpopulations, high (aminoglycosides, fluoroquinolones) and maintained (β-lactams) antibiotic concentrations are required in the infectious foci. Nevertheless, in certain infection sites (as in pneumonia in the intubated patient, ventriculitis, meningitis), even with the maximum tolerated dose, MPCs are not exceeded or the associated toxicity is unacceptably high. In these cases, the possibility of directly introducing the antibiotic into the infectious foci using the inhalatory, intrathecal or other routes (depending on the infection site) should be considered.

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