Strategies for antibiotic selection in empirical therapy

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The treatment of severe infections and particularly of nosocomial infections should be based on an accurate strategy: in the first phase, cultures should be made in order to target the antibiotic therapy; then, it is important to begin an empirical therapy, especially against Gram-negative bacteria, which are responsible for many severe infections, and where delayed therapy is related to increased mortality.

Empirical therapy should consider the following:

- site of infection;
- anamnestical and epidemiological data about probable etiology;
- *in vitro* sensitivity of pathogens according to local epidemiology;
- pharmacokinetic properties of antibiotics, such as tissue distribution.

The choice of empirical antibiotic therapy must consider the following:

- type of microorganism;
- site of infection;
- host characteristics.

With regard to microorganisms, we must consider that antibiotic resistance progressively increases with the use, sometimes irrational, of these drugs. Particular problems are posed by β-lactamase producers, fermenting and nonfermenting Gram-negative bacteria, methicillin-resistant staphylococci and glycopeptide-resistant enterococci.

When considering the site of infection, we must consider the factors reported in Table 1. An example of a physiological barrier is the blood–bronchi barrier: the antibiotic diffusion in the respiratory tract is summarized in Table 2.

The choice of antibiotic is also related to underlying diseases in the host: immunodeficiency due to HIV, cancer, chemotherapy, steroids, transplants, burns, severe trauma, organ failure, allergy, genetic factors.

Adequate empirical therapy must be early, broad spectrum, highly distributed, rapidly bactericidal and prolonged.

Bactericidal activity may be important: the most rapid bactericidal agents are aminoglycosides and fluoroquinolones, while β-lactams are more slowly bactericidal [1].

Optimization of empirical therapy for severe infections is a very difficult challenge because of increasing bacterial

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Table 1 Choice of empirical therapy, factors related to the site of infection

Barriers to antibiotic diffusion
Blood–brain
Blood–bronchi
Blood–prostate
Presence of foreign bodies
Intravascular catheters
Urinary catheters
Prostheses
Slime production (staphylococci, with adherence to prosthetic surfaces)

Table 2 Penetration of antibiotics in the respiratory tract

Fluoroquinolones*	+ + +
Carbapenems	+ / + +
Broad spectrum cephalosporins	+ / + +
Ureidopenicillins	+
Aminoglycosides**	–

*High intracellular concentration. **Inactivated by the low pH of bronchial secretion.

Table 3 Antimicrobial resistance: current problems

Antibiotic	Resistance problem
Penicillins	Methicillin-resistant *S. aureus*
	Penicillin-resistant *S. pneumoniae*
	Ampicillin-resistant *H. influenzae*
β-lactamase inhibitors	Enterobacteria hyperproducing βIs*
Cephalosporins	Enterobacteria and *P. aeruginosa* hyperproducing chromosomal βIs
Carbapenems	Nonfermenters producing zinc enzymes
Aminoglycosides	Organisms producing modifying enzymes
Fluoroquinolones	Quinolone-resistant *Escherichia coli*, *S. aureus*

*βIs, β-lactamases.

Table 4 Antimicrobial resistance: emerging problems

Gram-positive organisms	Resistance problem
S. pneumoniae	Third generation cephalosporins resistance
	Low-level macrolides resistance
β-hemolytic streptococci	Erythromycin resistance
Enterococcus spp.	Vancomycin-teicoplanin resistance
S. aureus	Vancomycin/hetero-resistance (VISA)
Gram-negative organisms	Resistance mechanisms
Enterobacteriaceae	Extended-spectrum β-lactamases (ES βl)
	β-lactamases resistant to inhibitors (IRT)
Enterobacteriaceae	New ES βl (OXA-, chromosomal-derived)
P. aeruginosa	Plasmid-mediated carbapenemases
	Multidrug efflux resistance mechanisms
	Interplay of different resistance mechanisms
Acinetobacter baumanii	Novel β-lactam hydrolyzing enzymes
Stenotrophomonas maltophilia	Multiple-antibiotic-resistant dissemination
Burkholderia cepacia	Multiple-antibiotic-resistant dissemination
Bacteroides fragilis	New carbapenem hydrolyzing enzymes

resistance to antibiotics, often due to their inappropriate use. Current resistances involve most antibiotic classes (Table 3).

Resistance is emerging in both Gram-positive and Gram-negative microorganisms, based on various mechanisms (Table 4).

Previous experience suggests that empirical therapy of severe infections should be based on a combination of broad spectrum β-lactams plus aminoglycosides, or a monotherapy with fluoroquinolones, carbapenems or fourth-generation cephalosporins [1].

In combination therapy it is advisable to employ broad-spectrum cephalosporins because their pharmacokinetic activity in the respiratory tract is superior to that of penicillins and those of aminoglycosides less susceptible to enzyme inactivation (amikacin).

The use of third-generation cephalosporins in the last 10 years has contributed to the spread of extended-spectrum β-lactamase producers and an increasing number of nonfermenting multidrug-resistant Gram-negative strains with many potential problems (Table 5).

Table 5 Potential problems with third-generation cephalosporins

Suboptimal activity against Gram-positive organisms
Emergence of penicillin-resistant viridans sterptococci
Bush group 1 β-lactamase-producing bacteria (*Enterobacter*, etc.)
Bacteria producing ES βls*
Resistance among nonfermenters

*ES βls, extended-spectrum β-lactamases.

Fluoroquinolones have good pharmacokinetic characteristics, especially in the respiratory tract, and rapid bactericidal activity, but their use in monotherapy is not advisable because of the risk of emergence of resistant staphylococci and *E. coli*.

Another alternative choice is offered by carbapenems, although extended use of these has raised important epidemiological and pharmaco-economic concerns.

Particular attention should be given to fourth-generation cephalosporins in the treatment of severe infections, particularly those due to Gram-negative bacteria. Clinical results from international trials have proved the effectiveness of cefepime in severe nosocomial infections, in febrile neutropenic patients and in LRTI [2–4].

In neutropenic patients and in general in severe infections, cefepime presents a greater anti-Gram-positive activity (except against MRSA) than do other antipseudomonal cephalosporins, a greater efficacy against β-lactamase group 1 and extended-spectrum β-lactamase producers, and efficacy against many nonfermenting bacteria [5].

In neutropenic patients, cefepime represents a currently accepted empirical therapy alternative to ceftazidime and penicillins plus aminoglycoside as documented in many international trials [4,6].

Cefepime efficacy in proven or suspected septicemia is comparable with ceftazidime in many studies. Cefepime efficacy in LRTI is comparable with ceftazidime and cefotaxime [2,3]. Therefore, cefepime is an effective alternative to third-generation cephalosporins in empirical therapy of febrile neutropenia, presumptive and established nosocomial septicemia, in LRTI, in complicated UTIs, skin and soft-tissue infections, and in meningitis [7,8].

On the basis of these considerations, and of our experience, we can suggest a schedule for empirical therapy of severe infections. Our choice, where there is a high incidence of resistant strains, is a fourth-generation cephalosporin plus an aminoglycoside, for the better efficacy of fourth-generation cephalosporins *vs.* fermenting and nonfermenting Gram-negative bacteria. Monotherapy is possible, but there are a few problems, such as possible resistance to fluoroquinolones and epidemiological-pharmacoeconomic problems for carbapenems. Moreover, for a safer use of fourth-generation cephalosporins, we prefer to employ them in association with an aminoglycoside, in the treatment of severe infections, particularly in children and in compromised patients.

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