

## Leading articles

### Prescribing guidelines for severe *Pseudomonas* infections

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Almost 50 years ago, *Pseudomonas aeruginosa* was rarely considered as a real pathogen. In the 1970s it was recognized as the microorganism associated with bacteraemia in the neutropenic host. Nowadays, it is among the most common pathogens involved in nosocomial infections. Hospital reservoirs of the microorganism include respiratory equipment, antiseptics, soap, sinks, mops, hot tubs, artificial fingernails, and physiotherapy and hydrotherapy pools.<sup>1</sup> In addition, the lower respiratory tract of mechanically ventilated patients, the gastrointestinal tract of patients on anticancer chemotherapy, as well as any mucosa and the skin of hospitalized patients treated with broad-spectrum antibiotics, can be colonized with *P. aeruginosa* at rates exceeding 50%.<sup>1</sup> The hands of hospital personnel serve as the bridge between the inanimate and animate environments.<sup>2,3</sup>

The physician of the new millenium should consider that *P. aeruginosa* will continue to belong among the major virulent pathogens implicated in the following major syndromes:<sup>1,4–6</sup> (i) pneumonia in mechanically ventilated patients (VAP) and in the neutropenic host; (ii) exacerbations of cystic fibrosis; (iii) primary bacteraemia in neutropenics and HIV-infected individuals with CD4 <50 cells/mm<sup>3</sup>; (iv) right-sided native valve endocarditis in iv drug users and left-sided early prosthetic valve endocarditis; (v) malignant external otitis in diabetics; (vi) nosocomial meningitis and brain abscesses after neurosurgery and fractures of the base of the skull; (vii) endophthalmitis complicating penetrating injuries, intraocular surgery and contaminated artificial lenses; (viii) osteomyelitis due to haematogenous spread, trauma and orthopaedic surgery whenever prosthesis are implanted; and (ix) soft tissue infections complicating severe burns. Swimmer's ear and vesicular or maculopapular skin lesions connected with inadequately chlorinated swimming pool water represent mild *P. aeruginosa* infections, which do not require systemic therapy.

In order to apply optimal therapeutic guidelines, which considerations and questions require thoughtful answers

before the physician of the new millenium prescribes an antipseudomonal antibiotic?

Awareness of the recent epidemiological data is of major importance. In the EPIC study,<sup>7</sup> *P. aeruginosa* was recognized as the predominant Gram-negative species (28.7%) isolated from bronchopulmonary infection sites of patients hospitalized in 1417 intensive care units (ICUs) of 17 Western European countries.

According to the NNIS study,<sup>8</sup> out of 39 810 isolates collected in the USA between 1990 and 1999, *P. aeruginosa* predominated (17%) among Gram-negatives associated with hospital-acquired ICU pneumonia. In the most recent SENTRY study,<sup>9</sup> performed in 1997 in Canada, USA and Latin America, among 4267 blood stream isolates *P. aeruginosa* was the third most common pathogen (10.6%). However, it should be pointed out that through the years, blood isolates of *P. aeruginosa* are decreasing in the febrile neutropenic host. Instead, Gram-positives are increasing in frequency, mainly because of the increasing use of central venous catheters and oral prophylaxis with quinolones.<sup>10,11</sup>

Physicians should always consider that *P. aeruginosa* is a lethal pathogen, with 34% of bacteraemia mortality attributable to it,<sup>12,13</sup> a crude mortality of 50% in the bacteraemic neutropenic host and an overall mortality of 45% and 69%, respectively, in bacteraemic nosocomial pneumonia and VAP.<sup>14,15</sup> Increased mortality has been attributed to:<sup>1,15</sup> (i) the elaboration of a mucoid exopolysaccharide that offers protection from host immune factors, particularly in patients with cystic fibrosis; (ii) the production of a wide variety of enzymes and toxins responsible for tissue destruction and bacterial invasion; (iii) the vulnerability of the immunocompromised host; and (iv) the worldwide emergence of multidrug-resistant nosocomial clones. Current global cumulative resistance surveillance data, derived mostly from ICU patients, are alarming (Table).<sup>7,9,16</sup> On the other hand, the emergence of resistant strains during therapy is associated with: (i) a three-fold increase in mortality; (ii) a nine-fold higher rate of

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**Table.** Surveillance studies of *P. aeruginosa* resistance

Study	Year [Ref.]	Country	n <sup>a</sup>	Resistance rates to the indicated antimicrobial (%)						
				gentamicin	amikacin	piperacillin	ceftazidime	ciprofloxacin	imipenem	meropenem
EPIC study	1992 [7]	Europe	410	46.3	NA <sup>b</sup>	37.4	27.7	26.3	21.1	NA
SENTRY study	1997 [9]	USA	276	12	3	9	13	15	11	5
		Canada	83	16	5	4	12	12	19	6
		Latin America	92	28	16	20	14	26	15	5
		Greece <sup>c</sup>	1704	32	63	37	45	75	64	48
MYSTIC study	1999–2000 [16]	USA–Mexico	276	23	NA	14	21	18	24	22
		Europe	782	46	NA	18	30	30	31	21
		Middle East + Asia	62	29	NA	11	24	30	42	10

<sup>a</sup>Number of strains tested.

<sup>b</sup>NA, not available.

<sup>c</sup>Seventeen ICUs (N. Legakis and A. Vatopoulos, personal communication).

secondary bacteraemia; (iii) a 2.1-fold increase in length of hospital stay; and (iv) an increase of total hospital charges by \$11 981.<sup>17</sup> Therefore, the necessity of obtaining reliable cultures is obvious, particularly in the ICU patient with VAP. Quantitative bronchial secretion cultures and cultures obtained after performing protected bronchoalveolar lavage (BAL), protected specimen brushing or even the non-bronchoscopic mini-BAL are now considered indispensable.<sup>18,19</sup>

What rational therapeutic guidelines and antibiotic policies should the physician follow in order to treat *P. aeruginosa* infections successfully? The array of available antibiotics with antipseudomonal activity includes the aminoglycosides, ticarcillin, ureidopenicillins, ceftazidime, cefepime, aztreonam, the carbapenems and ciprofloxacin.<sup>20</sup> However, there is no evidence that newer antipseudomonal antibiotics active against multidrug-resistant clones will appear in the future.<sup>21</sup> Patients infected with *P. aeruginosa* in the new millennium should survive given the existing antibiotics.

While awaiting culture results, therapeutic selection should initially be empirical based on the severity of the infection, underlying risk factors and diseases, knowledge of epidemiology and resistance phenotypes in individual settings, and the required pharmacokinetic–pharmacodynamic parameters. Unfortunately, in hospitals with a high prevalence of multidrug-resistant *P. aeruginosa*, colistimethanate sodium, the old neurotoxic and nephrotoxic antibiotic of the 1950s, has been rediscovered by intensivists.<sup>22</sup> To overcome its kinetic disadvantages and toxicity, aerosolized colistin was recently given successfully for nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant strains.<sup>23</sup>

Can the development of resistance be prevented, or at least the existing resistance rates be diminished? The shortest possible duration of therapy plus high dosing of ciprofloxacin to achieve an AUIC  $\geq$  250, as well as the administration of the optimal  $\beta$ -lactam dose at frequent intervals to achieve plasma levels exceeding MICs against *Pseudomonas* for an adequate length of time between doses (40%), should lower the risk of resistance emerging.<sup>24–27</sup> For the aminoglycosides and the newer fluoroquinolones, an inhibitory quotient ( $C_{\max}/MIC$ ) of  $>10$ , depending on the height of their peak levels, is connected with optimal efficacy. Recently, the *in vitro* estimation of the mutation prevention concentration (MPC) was described for the newer fluoroquinolones and *Streptococcus pneumoniae*.<sup>28</sup> However, its validation against *P. aeruginosa*, which should be of importance, is still awaited.

It seems that certain antibiotics are more prone to developing resistance during therapy, leading to treatment failures.<sup>29</sup> In three well controlled studies comparing imipenem with ceftazidime, ciprofloxacin or piperacillin/tazobactam, imipenem was less effective than ceftazidime or ciprofloxacin in patients with *P. aeruginosa* pneumonia.<sup>30–32</sup> In all studies, the development of resistance to

imipenem (c. 50%) explained the lower efficacy of the drug. Imipenem was found by Carmeli *et al.*<sup>17</sup> to possess an adjusted hazard ratio for resistance development in *P. aeruginosa* strains of 2.8 ( $P = 0.02$ ), compared with 0.7 for ceftazidime, 0.8 for ciprofloxacin and 1.7 for piperacillin. The same investigators have suggested that the use of imipenem for treatment of *P. aeruginosa* infections should be reserved for isolates resistant to other antibiotics. At the molecular level, the selected imipenem-resistant strains mainly represent impermeability OprD<sup>-</sup> mutants, which have a narrow-spectrum non-susceptibility to other classes of antipseudomonal drugs. On the other hand, meropenem resistance co-depends on upregulation of the MexA-MexB-OprM efflux system, a mechanism that is more difficult for the microorganism to achieve.<sup>33</sup> It represents a multidrug efflux pump, which in *P. aeruginosa* confers cross-resistance to both fluoroquinolones and all  $\beta$ -lactams. In Mediterranean countries, emerging *P. aeruginosa* multidrug-resistant clones may produce the plasmid VIM metallo- $\beta$ -lactamases, which, like IMP-1, hydrolyse all  $\beta$ -lactams, with the exception of aztreonam<sup>34–36</sup> (unpublished observations). These findings present a rational justification for not empirically prescribing carbapenems as first choice antibiotics.

Can the physician improve therapeutic results by prescribing a combination of antipseudomonal antibiotics?<sup>37</sup> *In vitro* synergic results for amikacin plus ceftazidime or a carbapenem, as well as for imipenem with ciprofloxacin, were found to be promising and independent of the MICs of the interacting antibiotics.<sup>38–40</sup> *In vivo* studies performed in the 1980s showed that survival of neutropenic bacteraemic hosts was better when gentamicin was combined with carbenicillin or ticarcillin.<sup>13</sup> Physicians, based on tradition, still very often prescribe the combination of an antipseudomonal  $\beta$ -lactam plus an aminoglycoside for serious *P. aeruginosa* infections, particularly in the febrile neutropenic host.<sup>10</sup> Current studies in *P. aeruginosa* VAP, however, show the same failure rates whether or not imipenem or ciprofloxacin is combined with an aminoglycoside. Depending on the depth of neutropenia and physical symptoms, the need for a second drug has been questioned,<sup>12,30–32,37,41</sup> even in neutropenic patients. On the other hand, in *P. aeruginosa* bacteraemia the survival rate was no greater in patients who received two or more antibiotics active *in vitro* against *P. aeruginosa* than in those who received only one (86% versus 87%).<sup>12</sup> Unfortunately, no prospective, randomized comparison between monotherapy and combination drug therapy has been performed in a large number of neutropenic or ICU patients with *Pseudomonas* bacteraemia, sepsis or VAP.

There is no doubt that antipseudomonal antibiotic overuse and misuse are strongly connected with the emergence of multidrug-resistant *P. aeruginosa*.<sup>42</sup> In the effort to improve therapeutic results while preserving the power of newer antibiotics, Trouillet *et al.*<sup>43</sup> developed a rational algorithm to be used in the ICU. They determined that the

initial decision of empirical therapy in ICU patients with VAP is greatly influenced by: (i) prior broad-spectrum antimicrobial therapy in the 2 weeks preceding VAP that was connected to the isolation of multidrug-resistant *P. aeruginosa*; and (ii) the duration of mechanical ventilation ( $\geq 7$  days: late onset). According to the latter study, only in late-onset VAP with previous antibiotics use is the empirical prescription of a carbapenem justified. In case of early-onset pneumonia with prior antibiotics or late-onset pneumonia without prior antibiotics, an antipseudomonal cephalosporin or piperacillin/tazobactam plus an aminoglycoside should be the rational choice.

Should infectious disease physicians and intensivists expect that 'antibiotic cycling' in the ICU will prevent or reduce resistance?<sup>44</sup> The so-called 'continuous rotational therapy' in the ICU seems to provide the best chance for combating the emergence of resistance.<sup>45</sup> This policy, based on the bacterial ecology of each ICU, allows for the use of different classes of antibiotics at predetermined time intervals, though the physician's choice may be influenced by the regimen that each patient has received previously.<sup>45</sup> Gruson *et al.*,<sup>46</sup> based on the bacterial ecology of their ICU, applied a programme of supervised rotation plus restricted use of ceftazidime and ciprofloxacin in order to minimize the incidence of VAP caused by microorganisms resistant to the latter antimicrobials. After a 2 year period, a significant decrease in the total number of antibiotic-resistant Gram-negatives, as well as a significant increase in the susceptibilities of *P. aeruginosa* to several antipseudomonal antimicrobials, was observed.

Finally, it is needless to underline the importance of strict handwashing or of the appropriate use of antiseptics and gloves in order to escape the horizontal transmission of multiresistant *Pseudomonas* clones.<sup>2,3</sup>

Approaching the officially predicted 'end of antibiotics',<sup>21</sup> the physician, whenever prescribing an antipseudomonal antibiotic, should always consider the following:

1. Local resistance surveillance data and resistance phenotypes.
2. The source of the infection, i.e. community acquired versus nosocomial.
3. The existence of major underlying risk factors, i.e. neutropenia and mechanical ventilation.
4. The length of hospitalization and of mechanical ventilation.
5. The type of antimicrobials administered in the recent past.
6. The required pharmacokinetic and pharmacodynamic parameters, aiming to achieve the highest efficacy while avoiding emergence of resistance during therapy.
7. The possibility of obtaining *in vitro* synergy with a combination of antipseudomonal antimicrobials.
8. The *in vivo* results of advanced antipseudomonal monotherapy versus combination therapy with antipseudomonal  $\beta$ -lactams plus an aminoglycoside.
9. The application of 'therapeutic consensus agreements'

against *P. aeruginosa* based on either restriction of selected antibiotics and/or continuous rotational policies tailored to each institution.

There is presently no reason to doubt that strategies of optimal prescribing, including control of antibiotic use, should be a leading priority in the effort to improve therapeutic outcomes in pseudomonal infections. It is certain that if the new millennium physician does not cut back on the use of antibiotics, the emerging resistance problem of *Pseudomonas* will worsen while the approaching era of 'the end of antipseudomonal antibiotics' will become a nosocomial nightmare.

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