Traitement et pronostic des bactériémies à Pseudomonas aeruginosa

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TRAITEMENT ET PRONOSTIC DES BACTERIEMIES

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TO ADIL

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INTRODUCTION

A) MICROBIOLOGY

Pseudomonas aeruginosa (in latin: *aeruginosus* meaning "covered in rust") is a member of the *Pseudomonadaceae* family. This Gram-negative rod is motile, grows aerobically, and produces a characteristic sweet grape odor in culture. It is ubiquitous and is therefore found in a wide range of places, but with a predilection for moist environments such as water, soil, plants and raw vegetables,(e.g. salads). In hospitals, respiratory equipments, physiotherapy pools, disinfectants, sinks, flowers and mops can be reservoirs for *P. aeruginosa*.

P. aeruginosa is an opportunistic human pathogen, almost exclusively infecting patients with an underlying immunosuppression, ranging from neutropenic cancer patients to critically ill mechanically ventilated patients. In fact, it is considered to be the prototype of "the hospital bacteria". *P. aeruginosa* can produce a wide range of infections in humans, the most important being nosocomial pneumonia. *P. aeruginosa* is one of the most common causes of ventilator associated pneumonia (VAP) in intubated patients (1,2). It is also responsible for nosocomial urinary tract infections and bacteremia. It is less frequently responsible for surgical or burn wounds infections, malignant external otitis in diabetics, gastrointestinal infections such as abscesses, cholangitis, peritonitis, pancreatitis, osteomyelitis, keratitis (panophtalmitis) and finally endocarditis in iv drug users.

P. aeruginosa owes its pathogenic potential to several features. This bacteria produces an important number of virulence factors, which are either cell-associated, such as the flagellum, the pili, the LPS and an extracellular matrix called biofilm, or secreted compounds having a specific enzymatic activity. More then half of the clinical isolates produce the fluorescent pigment pyocyanin.

Implanted in the external membrane are the polar flagella and pili, which are not only responsible for motility but also play a role in adhesion to mucosal membranes (3), and the lipopolysacharides, which are macromolecular complexes also called endotoxin, responsible for the induction of the major inflammatory host response. Under certain conditions, *P. aeruginosa* produces an extracellular matrix, referred to as the biofilm. This matrix is essential for colonisation of inert

surfaces and might also play a role in the interaction with epithelial cells. In the specific lung environment of cystic fibrosis patients, *P. aeruginosa* forms so called mucoid colonies that produce a very thick and slimy matrix consisting of mannuronic and guluronic acid in a repeating structure that is termed alginate. These mucoid strains are known to be more resistant to phagocytosis and less susceptible to antibiotic killing (4).

P. aeruginosa also produces a number of secreted virulence factors. The proteases, mainly elastase and alkaline protease, play an important role during tissue invasion, for example, by degrading elastin fibers in lung tissue, as well as laminin and elastin fibers in the basal membrane of vascular tissue, and destroying connections between cells, such as in the cornea and the human respiratory epithelium. The hemolysins, rhamnolipids and phospholipase C, also contribute to tissue destruction, owing to their cytotoxic action and their potential for degrading the lung's surfactant. They work in a synergistic manner: rhamnolipids solubilise lipids, thereby facilitating the action of phospholipase C which hydrolyses the phospholipids of cytoplasmic membranes. Exotoxine A plays a role in the systemic toxicity of *P. aeruginosa*, by inhibiting protein synthesis in a similar way to the diphteria toxin. The expression of several of these exoproducts is regulated and coordinated by sophisticated cell-to-cell signaling systems modulated by cell density (the quorum-sensing phenomenon) (3). Their phenotypic expression also varies according to their site of isolation (6).

On top of these, *P. aeruginosa*, like other Gram-negative bacteria, produces a special secretion system, named type III secretion system, which serves to inject toxins directly into adjacent host cells. It consists of three coordinately functioning protein complexes, namely the secretion and translocation apparatus and the secreted toxins themselves, which in the case of *P. aeruginosa* are called ExoS, ExoT, ExoU and ExoY. It has been recently determined that the expression of these type III secretory proteins in respiratory isolates is associated with the patient's death and an increased morbidity (this is to say higher probability of hospitalisation, pneumonia and sepsis) (5).

It is important to stress that *P. aeruginosa* infections are difficult to treat because of the bacteria's intrinsic resistance to many antibiotics, owing to its low outer membrane permeability, and its ability to acquire new resistance mechanisms during antibiotic treatment. *P. aeruginosa's* broad spectrum of resistance relies on a wide range of different mechanisms, which are either encoded in its own chromosome or on plasmids. Resistance to most penicillins is produced by constitutive or inducible b-lactamases. They bind the b-lactam molecules much stronger than the penicillin binding proteins (PBP) and hydrolyse them by opening the b-lactam cycle. Secondly, *P. aeruginosa* is also

capable of modifying the PBF. Lastly it can use an efflux system "Mex-AB-Opr M", which is expressed constitutively to expulse the b-lactam molecule out of the cell (7)."Mex-AB-OprM" is part of five efflux systems, which are constructed on the same model, by *P. aeruginosa*. They are made out of three different proteins, which work together. The first, an inner membrane protein, acts as a proton motor pump. The second, a periplasmic protein, links the first to the third component of the system, which is an outer membrane protein acting as an efflux porin. It's important to stress the fact that each efflux system is able to accommodate compounds structurally unrelated, such as antibiotics of completely different classes, consequently inducing multiple resistance profiles (8).

The resistance to third and fourth generation cephalosporins is based on the same mechanisms, except for the fact that the efflux system dealing with fourth generation cephalosporins is slightly different and its expression is only inducible. It is named "Mex-CD-Opr J". The resistance to carbapenems, imipenem and meropenem, is mainly due to the loss of a specific outer membrane protein (porin) called OprD, a highly selective permeation pathway (9). Resistance to quinolones is also mediated by several mechanisms: three out of the four efflux systems can expulse these molecules, the constitutive "MexAB-M", and the inducible "MexCD-J" and "MexEF-N". Their activation usually precedes the selection of a mutation of the DNA gyrase, which is the quinolone target (8). Aminoglycosids are rendered ineffective either by mutation of the ribosomal 30S gene, which encodes the antibiotic target protein; or by the constitutive expression of the efflux system "Mex XY" as well as by the plasmid-encoded enzymatic activity of acetylation, phosphorylation or adenylation of the antibiotic (1,7).

Finally, resistance to macrolids is due to the efflux system "MexCD-J" and resistance to TMP-S to three of the pomps "MexAB-M", "MexCD-J" and "Mex EF-N".

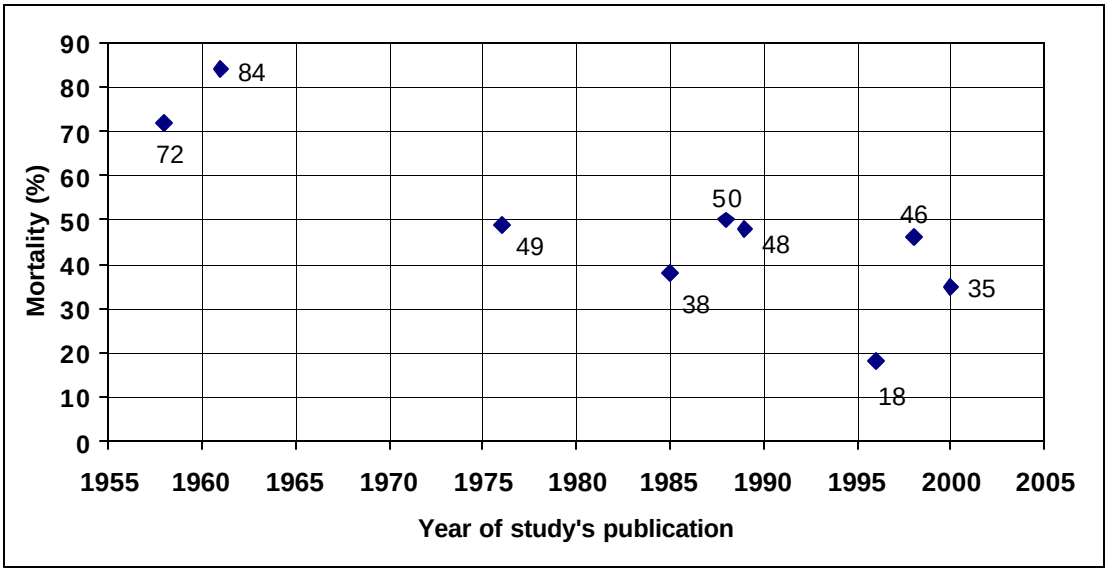
In conclusion this opportunistic bacteria, mainly responsible for nosocomial infections in debilitated patients, not only produces a number of cell-associated or extracellular virulence factors engaged in colonisation and tissue invasion, but also a wide variety of ingenious antibiotic resistance mechanisms which makes it a major therapeutic challenge.

B) *P. AERUGINOSA* BACTEREMIA

In spite of the fact that *P. aeruginosa* was recognized as a human pathogen in 1890 already, by Charing, it was not until the 1950's that physicians started to show a growing interest in *P. aeruginosa* bacteremia. Indeed Forkner noted in 1958 that "only scattered reports are available" describing *P. aeruginosa* septicemia and it's response to contemporary antimicrobial agents (10). From thereon the number of publications has been rising rapidly. Several important reasons explain this phenomenon, which we will now review.

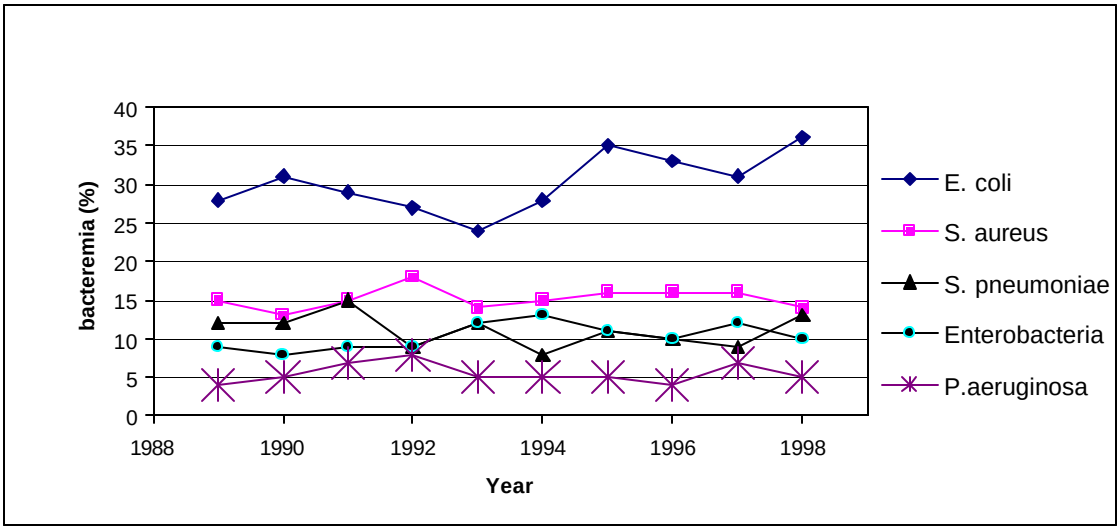
Mortality is certainly one of the reasons which led to an increasing attention towards *P. aeruginosa* bacteremia in the 1950's. Indeed the numbers are stunning: mortality reached 84% in a review by Curtin in 1961 (11). Nowadays death still occurs in one out of two patients (12), despite the fall in mortality noted in the 1970's, probably linked to the introduction of two potent anti-pseudomonal drugs in the late 60's, gentamicin and carbenicillin (figure 1). In the University Hospital of Geneva the mortality during the 1989-1998 period was found to be 25%.

Figure 1. Mortality linked to *P. aeruginosa* bacteremia



The rapidly rising incidence of *P. aeruginosa* bacteremia in the 60's and 70's has now placed it second amongst the Gram-negative bacteremia after *E. coli* (26); with a prevalence ranging from 1,8 to 4 ‰ (14,12). In the University Hospital of Geneva, the prevalence was found to be of 1‰ admissions and *P. aeruginosa* was the third most frequent cause of Gram negative bloodstream infection (1989 to 1998) (average 5,4% of all bacteremia per year) (figure 2). This is partly attributable to ecologic changes in the normal microflora of the human body provoked by the use of broad spectrum antimicrobial agents (11). It is also attributable to the improved management of many severe diseases leading to prolonged survival of patients to a point where their resistance to bacterial infections is greatly impaired. The larger use of more aggressive chemotherapy, radiotherapy, radical surgery and any instrumentation is also an important factor. Finally it has been mentioned that the emergence of AIDS in the 80's contributed to increase the rate of *P. aeruginosa* bacteremia (14)

Figure 2. Bacteremia at the University Hospital of Geneva



The fact that the number of antibiotics active against *P. aeruginosa* is limited, and tends to be even more so by the emergence of acquired resistance during therapy, is not the least important reason for the rising interest for *P. aeruginosa* bacteremia. In that sense *P. aeruginosa* occupies an almost unique position and certainly makes the choice of antibiotics very difficult (8). Especially as the administration of imipenem, ceftazidime and ciprofloxacin, all three potent antipseudomonal antibiotics, has recently been shown to lead to a higher risk of emergence of resistance to themselves (15). Moreover emergence of resistance is also associated with a longer stay in hospital, a trend

towards higher hospital costs and a higher rate of secondary bacteremia amongst patients infected by *P. aeruginosa* (16).

As mentioned before, *P. aeruginosa* is an increasingly prevalent nosocomial pathogen, but it is also an opportunistic one, making a rather specific group of patients at hight risk to develop a *P. aeruginosa* bacteremia. Nowadays, what was previously an event occurring in the very young or very old, most often affects middle age patients. As mentioned earlier, this evolution probably reflects the advances in medico-technical support, allowing prolonged survival of highly susceptible, critically ill patients such as patients with cancer, transplants, or burns (17). The average age found in most of the latest articles is 54 years with a predominance of men (14).

Most authors agree on a certain number of risk factors predisposing to *P. aeruginosa* bloodstream infections. The exposure to antibiotics up to four weeks before the event is found in 87% of patients (18). Usage of vascular catheters, urinary catheters and endotracheal intubation, present in 77%, 50% and 25 % respectively, have also been found to be risk factors in that they disrupt the integrity of the normal physical barriers, such as the epidermis or mucous membranes, and represent foreign bodies easily colonized by *P. aeruginosa*. Surgery, described in 34% of cases, also predisposes to *P. aeruginosa* bacteremia by the rupture of the physical barrier. Systemic corticotherapy, chemotherapy and neutropenia, described in 37%, 35% and 25% respectively, all contribute to immune deficiency, which is favorable to the occurrence of *P. aeruginosa* bacteremia. Finally, it was shown recently that secondary bacteremia developed significantly more often in patients infected by *P. aeruginosa*, in whom antibiotic resistance emerged (16).

The vast majority of patients who present a *P. aeruginosa* bacteremia have a severe underlying disease, most often cancer (29%), or a chronic disease (11%), such as diabetes, renal failure, cirrhosis, heart failure, chronic pancreatitis or COPD (14). As the proportion of *P. aeruginosa* bacteremia in patients with cancer has been growing recently, attention has been focused on this particular group of patients, unveiling the fact that hematological cancers (16% including leukemia and malignant lymphoma) are more common than solid tumors (13%) (14). Amongst hematological cancers the most frequent is leukemia whereas amongst the solid tumors, genitourinary cancers predominate (19). More recently, attention has turned towards solid organ transplantation (lung, kidney, liver, pancreas), and AIDS, as these have become important underlying diseases in patients developing *P. aeruginosa* bacteremia (14).

The usual path that leads to bacteremia starts by the patient being colonized. Then local infection occurs before the bacteria finally disseminates and causes a systemic illness. Unfortunately, it is not only almost impossible to predict the timing of these events but the source of the bacteremia frequently remains unknown (38%) (14). In the 60's, the most important identified primary site was the genitourinary tract (11). Nowadays, it has changed to pneumonia, owing to the greater awareness of the danger of urinary tract instrumentation, especially the use of urinary catheters and to improved, as well as prolonged respiratory support in severely ill patients (22% of urinary tract infections versus 48% of pneumonias in a recent study by Kuikka) (17). Vascular catheters are also important primary sites of infection (16%), as well as the digestive tract (deep abscesses 7%, pancreatitis 6%, peritonitis 6%, cholangitis or cholecystitis 5%) (14).

Unfortunately for the clinician there are no characteristic clinical features differentiating *P. aeruginosa* bacteremia from bacteremia due to other pathogens. The signs and symptoms range from fever (94%) (19) to septic shock (31-33%) (17-19) and rarely intravascular coagulation (0,5-11%) (19-17). The typical skin lesion "Ecthyma Gangrenosum" (a skin infarction progressing to large ulcerated gangrenous lesions, characterized histologically, by a bacterial invasion of vascular walls with minimal inflammatory infiltrate) seems to be a terminal sign. Prompt institution of appropriate antimicrobial therapy at the onset of the bacteremia accounts for the fact that such lesions are nowadays only rarely seen. The last mentions of this sign in the literature were 3% in 1976 (17), and 0,5% in 1985 (19).

Due to the high associated mortality, clinicians who deal with *P. aeruginosa* bacteremia are necessarily interested in establishing prognostic factors. Therefore, a number of studies have tried to determine and to validate such factors (12,14,17,23). In summary, receiving an inappropriate definitive antimicrobial therapy, presenting as a septic shock, having had a pneumonia as *P. aeruginosa* primary site of infection; having a severe underlying disease and being hospitalized in a surgical or ICU ward are all associated with a poor outcome. A higher risk of fatal outcome has also been noted in patients infected by *P. aeruginosa* and in whom resistance emerged (16). On the contrary, patients with high levels of antibodies against cytotoxins or the LPS have a better outcome (23). Neutropenia remains a subject of controversy as to it's influence on the patient's outcome; indeed some authors associate it with an increased mortality rate, whereas others do not confirm any significant impact on survival (21,14).

The choice between using an antipseudomonal monotherapy (antipseudomonal penicillin or fourth generation cephalosporin, carbapenems or ciprofloxacine) or a combination therapy

(traditionally a beta-lactam or carbapenem, combined with an aminoglycoside or ciprofloxacine) to treat an episode of *P. aeruginosa* bacteremia has also remained a controversy for many years. The idea of combining a beta-lactam and an aminoglycoside is based on *in vitro* synergistic results in the late seventies (2). In 1989, a prospective clinical study including 200 consecutive cases of *P. aeruginosa* bacteremias by Hilf *et al*. (21) supported the use of a combination therapy (simultaneous use of an aminoglycoside and a beta-lactam agent) rather than a monotherapy. Survival was indeed improved for the total patient study group and certain subgroups (patients with pneumonia as the primary site of infection; patients with bacteremia of nosocomial origin and critically-ill patients). More recently, Leibovici *et al*. in their prospective study on Gram-negative bacteremia in non-neutropenic patients (24), noted a trend towards a reduction of mortality in patients presenting a *P. aeruginosa* bloodstream infection when treated with a combination of a beta-lactam and an aminoglycoside. Possible explanations for this trend could be the avoidance of an inappropriate initial therapy against a resistant *P. aeruginosa* bacteremic strain or the selection during treatment of a resistant strain. Monotherapy regimens were indeed shown to have unacceptable failure rates when treating patients with *P. aeruginosa* pneumonia and the principle cause of failure was development of resistance during therapy (1). Theoretically the use of an empirical combination therapy before the results of the susceptibility tests are known should reduce the risk of failure, but this remains to be proven. As a reminder, *P. aeruginosa* is the most common Gram-negative pathogen isolated from patients receiving inadequate antimicrobial treatment (25).

Finally, it is important to keep in mind that *P. aeruginosa* bacteremia is not a rare infection, and that it is linked with a high mortality rate as still up to half of the patients die. The choice of an antimicrobial therapy is not only limited by the small number of antibiotics with an antipseudomonal activity but is made even more difficult by the ease with which resistant strains can be selected during therapy. Taking into account the fact that an inadequate definitive therapy is associated with a poor outcome, we undertook, at the University Hospital of Geneva, a large retrospective study on *P. aeruginosa* bacteremia. Our study was designed to address three controversial issues on *P. aeruginosa* bacteremia:

(1) Does exposure to antibiotics before the bacteremic event influence the resistance profile of the bacteremic strains *?*

(2) Does the adequacy of both empiric, and definitive therapy impact on mortality ?

(3) Does the use of a combination of two antipseudomonal antibiotics during empirical and/or definite therapy improve survival ?

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INTRODUCTION (VERSION FRANÇAISE)

A) MICROBIOLOGIE

Pseudomonas aeruginosa (en latin *: aeruginosus* signifiant recouvert de rouille) est un des membres de la famille des *Pseudomonaceae*. Ce bâtonnet Gram négatif est mobile, aérobie et produit une odeur caractéristique de raisin, en culture. C'est un germe ubiquitaire, que l'on retrouve partout, mais de manière privilégiée dans les milieux humides ou aqueux, tels les sols, les plantes, les végétaux (p.ex. les salades). En milieu hospitalier, on peut le mettre en évidence aussi bien dans les ventilateurs, les bassins de physiothérapie, les lavabos, que les produits de nettoyage et les plantes d'ornement.

P. aeruginosa est un pathogène opportuniste, infectant de manière presque exclusive les patients immunocompromis, par exemple neutropéniques, ventilés ou très gravement malades. En fait cette bactérie est décrite comme le prototype du germe hospitalier et est responsable d'un nombre important d'infections nosocomiales diverses et pouvant être sévères. C'est d'une part, un des germes le plus fréquemment retrouvé dans les cas de pneumonies associées à l'emploi d'une ventilation mécanique; d'autre part, il est responsable d'infections urinaires et de bactériémies; il est moins fréquemment associé à des infections de plaies chirurgicales ou de brûlures, d'otites malignes externes chez le patient diabétique, d'infections de la sphère gastro-intestinale tel qu'abcès intra-abdominal, cholangite, péritonite, pancréatite; enfin d'ostéomyélite, de kératite (panophtalmite) et finalement d'endocardite chez les patients toxicomanes.

P. aeruginosa doit son pouvoir pathogène à la production d'un nombre important de facteurs de virulence, qui sont soit directement associés à sa cellule, tels le flagelle, les pilli, le LPS et le biofilm, soit excrétés dans le milieu extra-cellulaire telles les diverses enzymes à activités spécifiques. Plus de la moitié des isolats cliniques produisent un pigment fluorescent nommé pyocyanine, qui donne aux colonies une couleur verdâtre. Le flagelle polaire, les pilli, et le LPS sont tous implantés dans la membrane externe de la cellule. Les premiers sont non seulement responsables de la mobilité de la cellule, mais également de son adhésion aux muqueuses, alors que le dernier, aussi appelé endotoxine, active la réaction inflammatoire de l'hôte. Dans certaines conditions, *P. aeruginosa*, produit une

matrice extra-cellulaire appelée biofilm. Celle-ci est essentielle à la colonisation des matières inertes et interagirait également avec les cellules épithéliales. Dans le cas particulier des patients présentant une mucoviscidose, les souches pulmonaires de *P. aeruginosa* forment des colonies mucoides qui produisent un biofilm très épais, qui consiste en une structure répétée d'acide manuronique et guluronique, se nommant alginate. Ces souches mucoides sont connues pour être particulièrement résistantes à la phagocytose et moins sensibles à l'action des antibiotiques. Comme mentionné ci-dessus, *P.aeruginosa*, produit aussi un certain nombres de facteurs de virulence excrétés dans le milieu environnant: les protéases, principalement l'élastase et la protéase alcaline, jouent un rôle important dans l'invasion tissulaire, par exemple en dégradant les fibres d'élastine du tissus pulmonaire, ou en détruisant la laminine et l'élastine des membranes basales, ou encore les connections intercellulaires au niveau de la cornée ou de l'épithélium respiratoire, par exemple. Les hémolysines, c'est-à-dire, les rhamnolipides et la phospholipase C, contribuent également à la destruction tissulaire grâce à leur action cytotoxique et à leur pouvoir de dégradation du surfactant pulmonaire. Ces enzymes travaillent de manière synergique: les rhamnolipides solubilisent les lipides membranaires libérant les phospholipides, qui sont hydrolysés secondairement par la phospholipases C. Quant à l'Exotoxine A, elle joue un rôle dans la toxicité systémique de *P. aeruginosa*, en inhibant la synthèse des protéines, à la manière de la toxine diphtérique. De plus, *P. aeruginosa*, comme d'autres Gram négatif, est pourvu d'un système spéciale de sécrétion appelé " type III secretion system", qui lui permet d'injecter des toxines directement dans la cellule hôte adjacente. Ce système est composé de trois protéines fonctionnant de manière coordonnée: le complexe de sécrétion et de translocation, ainsi que les diverses toxines, qui se nomment, dans le cas de *P. aeruginosa*, ExoS, ExoT, ExoU et ExoY. Récemment, il a été mis en évidence, que l'expression de ce système, au sein des isolats cliniques, est corrélée avec une augmentation de la morbidité et de la mortalité clinique (5).

La production de ces diverses enzymes extra-cellulaires est finement régulée et coordonnée par un système de signalisation intercellulaire modulé par la densité cellulaire (le phénomène de «quorum-sensing»).

Les infections à *P. aeruginosa* sont notoirement connues pour être difficile à traiter, en raison de la résistance intrinsèque de la bactérie à de nombreux antibiotiques, elle-même secondaire à la faible perméabilité de sa membrane externe et à son extraordinaire capacité d'acquérir de nouveaux mécanismes de résistance, en cours d'antibiothérapie. P. aeruginosa doit son large spectre de résistance à différents mécanismes, qui sont soit codés au niveau de son propre chromosome, soit sur des

plasmides. La résistance aux beta-lactams est principalement médiée par l'expression constitutive ou inductible de beta-lactamases. Celles-ci lient la molécule beta-lactam plus fortement que les PBP (penicillin binding protein), c'est-à-dire les protéines cibles de l'antibiotique et l'hydrolysent. De plus, *P. aeruginosa* est également capable de modifier la PBP. Enfin, la bactérie peut utiliser un système d'efflux «Mex-AB-OprM», qui est exprimé de manière constitutive, afin d'expulser la molécule de beta-lactam hors de la cellule.«Mex-AB-Opr M» fait partie d'un ensemble de cinq systèmes d'efflux, construits par *P. aeruginosa* sur le même modèle. Ils sont tous composés de trois protéines, qui fonctionnent de manière coordonnée. La première est une protéine s'insérant dans la membrane cytoplasmique et qui joue le rôle de pompe à proton (transporteur). La deuxième, une protéine périplasmique, relie la première à la troisième, qui est une protéine de la membrane externe, formant des pores et permettant le rejet des molécules pompées. Il est important de souligner, que chaque système d'efflux est capable d'accommoder des molécules structurellement non apparentées, tels des antibiotiques de différentes classes, entraînant, par conséquent, l'apparition de résistances multiples.

La résistance aux troisième et quatrième générations de céphalosporines se base sur les mêmes mécanismes. Néanmoins, le système d'efflux expulsant les céphalosporines de quatrième génération,«Mex-CD-Opr J », est légèrement différent et son expression n'est qu'inductible. La résistance aux carbapénèmes, imipenem et méropenem, est essentiellement due à la perte d'une protéine spécifique de la membrane externe, une porine appelée OprD, qui constitue un transporteur hautement sélectif.

La résistance aux quinolones est également médiée par divers mécanismes: trois des cinq pompes à efflux sont capables d'expulser ces molécules hors de la cellule:«Mex-AB-M», dont l'expression est constitutive et «Mex-CD-J», ainsi que «Mex-EF-N», dont l'expression est inductible. Leur activation précède généralement la mutation de la protéine cible des quinolones, c'est-à-dire la DNA gyrase. L'action des aminoglycosides est rendue caduque, soit par la mutation du gène codant pour la protéine 30S ribosomale, protéine cible de cette classe d'antibiotique, soit par l'expression constitutive de la pompe à efflux «Mex XY», soit, enfin, par l'acétylation-phosphorylation ou l'adélylation de l'antibiotique, par une enzyme codé au niveau d'un plasmide. Pour terminer, signalons que la résistance aux macrolides est due à l'expression du système «Mex-CD-J» et celle aux TMP-S à trois pompes «Mex-AB-M», «Mex-CD-J» et «Mex-EF-N».

En résumé, cette bactérie opportuniste, principalement responsable d'infections nosocomiales, chez les patients immunocompromis, produit non seulement des facteurs de virulence associés à sa cellule ou excrétés dans le milieu extra-cellulaire, responsables de la colonisation et de l'invasion tissulaire, mais également un nombre important de mécanismes de résistance aux antibiotiques, ce qui en fait un défit thérapeutique majeur.

B) BACTERIEMIE A *P. AERUGINOSA*

Malgré le fait que *P. aeruginosa* ait été reconnu comme pathogène humain en 1890 déjà, par un certain Charing, il faut attendre jusqu'en 1950 pour que le monde médical commence à s'intéresser sérieusement à cette bactérie. En 1958, Forkner notait qu'il n'existait que peu de rapports décrivant les bactériémies à *P. aeruginosa*. Dès lors, le nombre de publications n'a fait qu'augmenter. Plusieurs raisons importantes sont à la base de cet intérêt croissant. Nous allons en faire ici une revue.

En 1950, c'est la mortalité liée à la bactériémie à *P.aeruginosa*, qui est à l'origine de l'attention portée au sujet. Effectivement les chiffres sont alors impressionnants: le taux de mortalité pouvant s'élever jusqu'à 84% (revue par Curtin en 1961). De nos jours, près de la moitié des patients atteints peut encore décéder des suites de leur infection, malgré la baisse de la mortalité notée dans les années 70 et imputable à l'introduction de deux antibiotiques à action antipseudomonale: la gentamicine et la carbenicilline. A l'Hôpital Cantonal Universitaire de Genève, durant la période allant de 1989 à 1998, la mortalité s'élevait à 25%.

Les bactériémies à *P.aeruginosa*, se situent actuellement au deuxième rang des bactériémies à Gram négatif après celles à *E. coli*, avec une prévalence allant de 1,8 à 4‰, suivant les articles. A l'Hôpital Cantonal Universitaire de Genève, durant la période allant de 1989 à 1998, la prévalence était de 1‰, admissions et *P. aeruginosa* tenait le troisième rang des bactériémies à Gram négatif, avec une fréquence annuelle de 5,4%. Ceci reflète les changements apportés au sein de la microflore humaine, par l'utilisation de plus en plus fréquente d'antibiotiques à large spectre. Elle est aussi attribuable à l'amélioration de la prise en charge de patients gravement malades, dont la survie est prolongée au point ou leurs mécanismes de défense immunitaire sont compromis. Enfin, l'utilisation plus fréquente de chimiothérapie agressive, de radiothérapie et de chirurgie radicale sont également responsables de cette incidence sans oublier l'émergence du syndrome d'immunodéficience acquise, dans les années 1980.

Un autre point d'importance, responsable de l'intérêt croissant pour les bactériémies à *P. aeruginosa* est celui de la résistance de la bactérie aux antibiotiques. Le nombre d'antibiotiques actifs contre cette bactérie est encore restreint et l'est d'autant plus que la bactérie est capable d'acquérir de nouveaux méchanisme de résistances, en cours d'antibiothérapie. Dans ce sens, une étude récente a confirmé que l'administration d'imipenem, de ceftazidime et de ciprofloxacine, tous de puissants agents antipseudomonaux, est associé à un risque important d'émergence de résistance à ces mêmes antibiotiques. De plus, cette émergence de résistance, en cours de thérapie, parmi les patients infectés par *P. aeruginosa*, est associée à un séjour intra-hospitalier prolongé, à une tendance vers l'augmentation des coûts et à un risque de bactériémie secondaire.

Comme mentionné précédemment, *P. aeruginosa* n'est pas seulement un pathogène nosocomial, mais également un opportuniste, rendant certaines catégories de patients plus à risque que d'autre de présenter un épisode de bactériémie à *P. aeruginosa*. Ce qui était un événement touchant soit les patients très jeunes ou très âgés, intéresse les progrès médico-techniques, qui permettent de prolonger la survie de patients gravement malade, par exemple transplantés ou atteints d'un cancer.

La plupart des auteurs s'accordent sur le fait qu'il existe un certain nombre de facteurs de risque prédisposant à la survenue d'un épisode de bactériémie à *P. aeruginosa*: l'exposition à des antibiotiques, dans les quatres semaines préalables à l'épisode de bactériémie, est relevé chez 87% des patients; l'utilisation de cathéters endoveineux ou urinaires et l'intubation endotrachéale sont retrouvés chez 77%, 50% et 25% des patients respectivement. Leur mécanisme de facilitation repose sur la rupture de l'intégrité de la barrière physique de protection, tels les épithéliums ou les muqueuses, et la colonisation facilitée des matières inertes. Dans le même ordre d'idée, les gestes chirurgicaux, également relevés chez 34% des patients, prédisposent aussi à une bactériémie à *P. aeruginosa*. L'utilisation de corticoïdes systémiques, la chimiothérapie, et la neutropénie décrits dans 37%, 35% et 25% des patients respectivement, tous contribuent à une certaine déficience immunitaire favorable à la survenue d'une bactériémie à *P. aeruginosa*. Finalement, un article récent a démontré que les patients infectés par une souche de *P. aeruginosa*, chez qui une émergence de résistance aux antibiotiques avait été notée, présentaient significativement plus d'épisodes de bactériémies secondaires.

La majorité des patients présentant un épisode de bactériémie à *P. aeruginosa* sont sujets à d'importantes co-morbidités. Le plus souvent il s'agit de cancers (29%) ou d'une maladie chronique, telle le diabète, l'insuffisance rénale chronique, la cirrhose hépatique, l'insuffisance cardiaque, la pancréatite chronique ou la bronchopneumopathie chronique obstructive. Les cancers de la sphère

hématologique sont plus nombreux que les cancers touchant un organe solide (16% versus 13% des patients) et parmi les premiers, on trouve surtout des leucémies et moins des lymphomes; parmi les seconds, des tumeurs de la sphère uro-génitale prédominent. Notons, pour terminer, que les patients transplantés (poumons, reins, foie, pancréas) et les patients atteints du syndrome d'immunodéficience acquise forment des nouvelles catégories de patients à risque.

L'enchaînement des événements, qui mènent à une bactériémie, commence par la colonisation du patient. Une infection localisée survient ensuite, avant la dissémination systémique de la bactérie. Malheureusement, il est impossible de prédire le moment exact de ces différents événements et souvent le site primaire d'infection demeure inconnu (38% des cas). Dans les années 1960, le site primaire d'infection le plus souvent retrouvé était urinaire ; actuellement il est pulmonaire (22% des patients présentaient une origine urinaire et 48% une pneumonie, dans une étude récente). Ce changement est vraisemblablement secondaire à la prise de conscience du risque encouru lors d'instrumentation urinaire, ainsi qu'à la prolongation de la ventilation mécanique chez les patients sévèrement malades. Les cathéters endovasculaires sont également d'importants sites d'infection (16% des cas), ainsi que la sphère digestive (abcès intra-abdominal 7%; pancréatite 6%; cholangite ou cholecystite 5%).

Il faut déplorer l'absence de caractéristique clinique permettant de différencier une bactériémie à *P. aeruginosa*, d'une bactériémie due à un autre germe. Les symptômes et signes retrouvés dans la littérature s'échelonnent entre la fièvre (94% des cas) et le tableau de choc septique (ce dernier retrouvé dans 31% des cas en 1976 et 33% des cas en1985). Rarement il est fait mention d'une coagulation intraveineuse disséminée (11% en 1976 et 0,5% en 1985). La lésion cutanée typique nommée «ecthyma Gangrenosum» se caractérisant histologiquement par une invasion bactérienne de la paroi vasculaire, avec une réaction inflammatoire minime, progressant vers la nécrose cutanée et macroscopiquement visible sous forme de lésions ulcérées, semble être un signe terminal. L'introduction rapide d'une antibiothérapie explique probablement pourquoi cette lésion n'est plus guère retrouvée (3% de patients en 1976 et 0,5% en 1985, date de sa dernière mention dans la littérature).

Le clinicien qui traite une maladie aussi grave qu'une bactériémie à *P. aeruginosa* est nécessairement intéressé à établir des facteurs de pronostic, c'est pourquoi un certain nombre d'études ont été effectués, afin de les déterminer et les valider. En résumé, les facteurs de mortalité accrue sont les suivants: recevoir une antibiothérapie définitive inapproprié, une présentation initiale en choc septique, une bactériémie secondaire à une pneumonie à *P. aeruginosa*, des comorbidités sévère, enfin une hospitalisation en milieu de soins intensif de chirurgie. Un risque plus élevé de mortalité a

également été mis en évidence chez des patients infectés par des souches de *P. aeruginosa* devenues résistantes. Par contre, un risque moindre a été relevé chez des patients possédant de hauts taux d'anticorps contre les cytotoxines ou contre le LPS. De manière surprenante, la neutropénie demeure un sujet de controverse quant à son influence sur le pronostic final du patient; effectivement certains auteurs l'associent à une mortalité accrue, d'autres ne trouvent pas d'association significative avec l'évolution clinique.

Le choix entre l'emploi d'une monothérapie (généralement une pénicilline à effet antipseudomonal, une céphalosporine de quatrième génération,une carbapeneme, la ciprofloxacine) versus une combinaison de deux antibiotiques à effet antipseudomonal (traditionnellement une beta-lactam ou une carbapénème associé avec un aminoglycoside ou la ciprofloxacine) pour traiter un épisode de bactériémie à P. aeruginosa est un sujet de controverse depuis de nombreuses années. L'idée de combiner une B-lactam et une aminoglycoside est basée sur l'effet synergique obtenu in vitro, lors d'essai fait dans les années 1970. En 1989, une étude clinique prospective effectuée par Hilf *et a*l soutenait l'emploi d'une bithérapie (beta-lactam plus aminoglycoside), versus une monothérapie pour traiter une bactériémie à *P. aeruginosa*. Effectivement la survie de l'ensemble des patients de l'étude était améliorée. Ceci était particulièrement vrai pour certains sous-groupes, c'est-à-dire, les patients présentant une pneumonie comme site d'infection primaire, les patients dont l'épisode de bactériémie était nosocomiale et le groupe de patients sévèrement atteints.

Plus récemment, Leibovici *et al* ont mis en évidence, une diminution de la mortalité, parmi les patients non neutropénique, traités pour une bactériémie à *P. aeruginosa*, par une association de beta-lactam et d'aminoglycosides. Les raisons pouvant expliquer ce pronostic plus favorable sont, d'une part, le fait d'éviter d'employer une antibiothérapie inappropriée contre un germe résistant, d'autre part la réduction du risque de sélection d'un mutant résistant en cours de traitement. En 1992,une étude par Dunn *et al*. met en évidence un taux d'échec thérapeutique inacceptable parmi les patients traités par monothérapie pour une pneumonie à *P. aeruginosa*; la raison principale incriminée étant l'émergence de résistances parmi les souches bactériennes durant le traitement. Pour rappel, *P. aeruginosa* est le Gram négatif le plus fréquemment isolé chez les patients recevant une antibiothérapie inadéquate.

Pour terminer, il est important de rappeler les éléments suivants: la bactériémie à *P. aeruginosa* n'est pas un événement rare et la mortalité qui lui est associée est encore élevée, puisque certains articles rapportent que la moitié des patients atteints meurent encore de nos jours des suites de leur

infection. Le choix d'une antibiothérapie n'est pas seulement limité par le petit nombre d'antibiotiques à disposition ayant un effet antipseudomonal, mais est également rendu difficile par la facilité avec laquelle des souches résistantes sont sélectionnée durant une antibiothérapie. Et il est d'autant plus crucial de faire le bon choix, compte tenu du fait que l'administration d'une antibiothérapie définitive inadéquate est associée à un très mauvais pronostic. Au vu de l'importance du sujet, nous avons donc effectué une étude rétrospective sur les bactériémies à *P. aeruginosa*. Notre étude a pris place à l'Hôpital Cantonal Universitaire de Genève et s'est focalisée sur trois points encore débattus:

1) Est-ce que l'exposition à des antibiotiques à effet antipseudomonal, préalablement à l'épisode de bactériémie, influence le profil de résistance des souches bactériémiques?
2) Est-ce que l'adéquacité des traitements empiriques et définitifs influence la mortalité?
3) Est-ce que l'utilisation d'une antibiothérapie combinée comme traitement empirique ou définitif influence la survie?

MAJOR ARTICLE

Influence of Previous Exposure to Antibiotic Therapy on the Susceptibility Pattern of *Pseudomonas aeruginosa* Bacteremic Isolates

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Many patients who present with *Pseudomonas aeruginosa* bacteremia have been previously exposed to antibiotics. To assess whether resistance of bacteremic strains to antipseudomonal antibiotics (piperacillin, ceftazidime, imipenem, ciprofloxacin, or aminoglycosides) is associated with previous exposure to these drugs, a case-control study including 267 cases of *P. aeruginosa* bacteremia was conducted. Twenty-five percent of the episodes had been preceded by the exposure to an antipseudomonal antibiotic. Eighty-one strains were resistant to at least 1 antibiotic; 186 were susceptible to all drugs. Via univariate analysis, the risks of resistance to ceftazidime and imipenem were found to be significantly associated with previous receipt of these agents. Using multivariate analysis, exposure to any antipseudomonal antibiotic as a monotherapy was found to be associated with an increased risk of subsequent resistance to itself (odds ratio, 2.5; $P = .006$). Therefore, clinicians should avoid readministering previously prescribed antibiotics when initiating empiric therapies for possible *P. aeruginosa* bacteremia, especially when they have been given as monotherapies.

Pseudomonas aeruginosa is a leading cause of nosocomial bloodstream infections, ranking third among gram-negative bacteria, after *Escherichia coli* and *Klebsiella* species [1]. Despite improvement in recent years, the prognosis of *P. aeruginosa* bacteremia remains poor, with case-fatality rates of ⩾20% [2–5]. Factors that delay therapeutic improvements are the rapid course of the disease, the scarcity of antibiotics with antipseudomonal activity, and the ease with which the bacterium acquires new resistances during antibiotic therapy [6]. As a result of this capacity to rapidly acquire resistance mechanisms, *P. aeruginosa* bacteremia frequently follows other infections treatment with antibiotic regimen that include antipseudomonal drugs.

Because the symptoms of *P. aeruginosa* bacteremia are nonspecific, the initial antibiotic therapy for possible *P. aeruginosa* bacteremia is almost always empirical, with a pending identification of the responsible pathogen and an unknown antibiotic resistance profile. Inappropriate antibiotic treatment of bacteremia is associated with a significantly poorer outcome [7]. It is therefore important to determine whether recent exposure to antibiotics with antipseudomonal activity increases the risk of resistance of bacteremic strains to these agents [3]. Answering this question would help clinicians choose the most adequate empirical treatment in clinical situations that include *P. aeruginosa* bacteremia as a possible cause.

We identified 267 *P. aeruginosa* bacteremic events that occurred at a tertiary-care hospital and conducted

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a case-control study to determine whether recent exposure to antibiotics with antipseudomonal activity was associated with an increased risk of resistance toward these drugs.

PATIENTS AND METHODS

This study took place at the Geneva University Hospital, Switzerland, a 1000-bed tertiary-care teaching center that serves as a first-line medical center for an urban population of ~400,000 inhabitants and as a referral center for a larger population coming from both Switzerland and nearby France.

Study design. We used the microbiology laboratory database of the hospital to identify all inpatients that had had 1 or several blood cultures positive for *P. aeruginosa* from 1 January 1989 through 31 December 1998. Medical records were reviewed for information on demographic characteristics, clinical presentation of bacteremia, primary site of *P. aeruginosa* infection, underlying medical conditions, immunosuppression at the time of bacteremia, invasive procedures, laboratory results of antibiotic susceptibility, and recent antibiotic treatment including an agent with antipseudomonal activity. An "episode" of *P. aeruginosa* bacteremia was defined as a positive blood culture with this pathogen. "Previous monotherapy" was defined as a therapy that started within 30 days before the positive blood culture, included only 1 of the antipseudomonal antibiotics used in our institution (piperacillin, ceftazidime, imipenem, ciprofloxacin, gentamicin, and amikacin), was administered for >48 h, and was stopped <15 days before the bacteremia. "Previous combination therapy" was defined as follows: treatment was initiated within 30 days and stopped <15 days before the positive blood culture; it included the concomitant use for ⩾48 h of a β-lactam antibiotic, and either an aminoglycoside or ciprofloxacin, or the combination ciprofloxacin plus aminoglycoside, with an exposure to a single drug for no more than 48 h. All other patterns of antibiotic exposure were classed in the "no previous treatment" group. In a first analysis, "cases" were defined as episodes of bacteremia caused by a strain of *P. aeruginosa* resistant to at least 1 antipseudomonal antibiotic and "controls" as episodes involving strains susceptible to all 6 antibiotics. Three categories of exposure were examined: any previous combination therapy, any previous monotherapy, and no previous therapy. In subsequent analyses, cases were episodes caused by a strain resistant to 1 specified antibiotic, and controls were episodes caused by a strain susceptible to that same antibiotic; hence, bacteremic strains resistant to ⩾2 antibiotics contributed more than once to these analyses. Patients were considered exposed if they had received the specified antibiotic either as a monotherapy or as an agent included in a combination therapy.

Microbiology. A minimum of 2 pairs of blood cultures was performed at the time of presumed bacteremia. *P. aeruginosa* was identified at the laboratory of clinical microbiology via standard clinical microbiology methods [8]. Antimicrobial susceptibility was determined by disk diffusion methods according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) [9]. An isolate was considered susceptible, intermediate, or resistant according to the criteria of the NCCLS. The isolates with intermediate susceptibility were classified as resistant for analysis. No molecular typing was performed.

Statistical analysis. We calculated crude ORs and exact 95% CI to evaluate the potential relation between previous antipseudomonal therapy and resistance of the bacteremic strain. Two-tailed Fisher's exact tests were used for the comparison of proportions.

Multiple logistic regression was used to assess whether having received a previous monotherapy or combination therapy including a specific antipseudomonal agent were independent risk factors for resistance of the bacteremic isolate to that same agent. Because data were scarce, observations corresponding to all 6 antibiotics were pooled in a stratified model. Therefore, each episode of bacteremia contributed 5 times to the model (1 stratum per antibiotic); variance estimates were adjusted to reflect the resulting dependence among observations. Previous monotherapy and combination therapy were forced in the model; we further considered independent variables with $P <$ .2 in univariate logistic regression (data not shown). To limit the risk of overfitting, no interaction terms were tested. Regression analyses were performed by STATA version 6.0 (STATA Corporation).

RESULTS

Characteristics of bacteremic episodes. During the study period, 273 *P. aeruginosa* bacteremic episodes occurred in 267 patients. Computerized microbiological data and medical records were available for all patients. Four patients had 2 independent episodes of bloodstream infections separated by 14–69 days, and 1 person had 3 episodes over a period of 50 days. We report here on the 267 initial episodes of *P. aeruginosa* bacteremia.

The overall incidence of *P. aeruginosa* bacteremia at the Geneva University Hospital was 1 per 1000 admissions (range per year, 0.63‰–1.45‰). *P. aeruginosa* bacteremia accounted for 5.4% (range, 3.7%–7.6%) of all bloodstream infections. The mean age of the patients was 59 years (range, 1 day to 93 years; SD, 22 years), and approximately two-thirds were men (table 1). At the time of bacteremia, 32% of patients were hospitalized in acute-care and 14% in chronic-care medical services, 17% were in surgical wards, and 37% were in intensive care units (medical and surgical). The most common sites of primary infection were the respiratory and the urinary tracts; no source

Table 1. Univariate associations of clinical characteristics with resistance of *Pseudomonas aeruginosa* in 267 patients.

Characteristic	Total no. (%)	Resistance to antipseudomonal agents: ⩾1 resistance (cases; *n* = 81)	Resistance to antipseudomonal agents: No resistance (controls; *n* = 186)	OR (95% CI)	*P*
Previous antipseudomonal therapy[a]					
No	201 (75.3)	55	146	—	—
Yes	64 (24.0)	26	38	1.8 (0.96–3.4)	.09
Monotherapy	54 (20.2)	22	32	1.8 (0.92–3.6)	.07
Combination therapy[b]	10 (3.7)	4	6	1.8 (0.35–7.8)	.47
Age, years					
<65	132 (49.4)	44	88	—	—
⩾65	135 (50.6)	37	98	0.76 (0.43–1.3)	.35
Sex					
Male	195 (73.0)	59	136	—	—
Female	72 (27.0)	22	50	1.0 (0.53–1.9)	1.0
Calendar time					
1988–1992	126 (47.2)	27	99	—	—
1993–1998	141 (52.8)	54	87	2.3 (1.3–4.1)	.003
Ward					
Medical acute care	84 (31.5)	18	66	—	—
Other	183 (68.5)	63	120	1.9 (1.0–3.7)	.03
Primary site(s) of infection					
Unknown/other	142 (53.2)	38	104	—	—
Respiratory	47 (17.6)	16	31	1.4 (0.64–3.0)	.36
Urinary	46 (17.2)	20	26	2.1 (1.0–4.4)	.04
Digestive	24 (9.0)	9	15	1.6 (0.58–4.4)	.33
Vascular	17 (6.4)	3	14	0.59 (0.10–2.3)	.56
Cutaneous	13 (4.9)	2	11	0.50 (0.05–2.4)	.52
Clinical presentation					
Fever/simple sepsis	183 (68.5)	48	135	—	—
Severe sepsis	29 (10.9)	11	18	1.7 (0.68–4.2)	.26
Shock	55 (20.6)	22	33	1.9 (0.94–3.7)	.06
Underlying medical condition[c]					
No	34 (12.7)	11	23	—	—
Yes	233 (87.3)	70	163	0.9 (0.39–2.2)	.84
Immunological risk factor for infection					
None of the following	203 (76.0)	64	139	—	—
Neutropenia	48 (18.0)	10	38	0.57 (0.24–1.3)	.16
Steroid treatment	18 (6.7)	7	11	1.4 (0.43–4.1)	.60
Invasive procedures					
None of the following	48 (18.0)	7	41	—	—
Vascular catheter	205 (76.8)	68	137	2.9 (1.2–8.1)	.01
Urinary catheter	150 (56.2)	50	100	2.9 (1.2–8.3)	.02
Intubation	101 (37.8)	32	69	2.7 (1.0–7.5)	.03
Drainage tube	57 (21.3)	17	40	2.5 (0.86–7.8)	.10
Parenteral nutrition	38 (14.2)	14	24	3.4 (1.1–11.3)	.02
Other	95 (35.6)	31	64	2.8 (1.1–7.8)	.02

[a] Includes ceftazidime, piperacillin, imipenem, ciprofloxacin, an aminoglycoside, or some combination of these; 2 patients had received a combination therapy with 2 antipseudomonal agents preceded or followed by a monotherapy with a third agent.

[b] Two patients who had received monotherapy followed by combination therapy including other drugs were classified as having received combination therapy.

[c] Malignancy, AIDS, diabetes, pancreatitis, respiratory dysfunction, heart disease, renal failure, severe nonpseudomonal infection, or severe trauma.

of bacteremia could be identified in about half the patients. Severe sepsis was the initial manifestation of bloodstream infection in 11% of episodes and shock in 22%. Approximately 233 (90%) of 267 patients had severe underlying medical conditions: 91, malignancy (34%); 69, heart disease (26%); 58, respiratory dysfunction (22%); 51, nonpseudomonal severe infection (19%); 48, renal failure (18%); 29, diabetes (11%); 16, AIDS (6%); 14, severe trauma (5%); and 12, pancreatitis (4%). Immunosuppression was documented in 64 patients (24%) and invasive procedure that increased the risk of bacteremia in 219 (82%).

Sixty-six patients (24.7%) had been exposed to an antibiotic therapy active against *P. aeruginosa* (monotherapy, $n = 54$; combination therapy, $n = 8$; monotherapy followed by a combination therapy with 2 other agents, $n = 2$; table 1) before the bacteremic event. Of these regimens, 36 included imipenem; 9, piperacillin; 9, ciprofloxacin; 8, ceftazidime; and 32, an aminoglycoside (table 2). Of the 267 *P. aeruginosa* blood isolates, 15 were not tested for susceptibility to imipenem and 1 isolate was not tested for susceptibility to piperacillin. A total of 186 blood isolates (70%) were susceptible to all tested antibiotics, 35 (13%) were resistant to 1 antibiotic, 27 (10%) to 2 antibiotics, and 19 (7%) to ⩾3 antibiotics. Forty-three isolates (16%) were resistant to an aminoglycoside (gentamicin or amikacin), 41 (15%) to imipenem, 29 (11%) to piperacillin, 16 (6%) to ceftazidime, and 15 (6%) to ciprofloxacin.

Univariate risk factors for resistance to ⩾1 antipseudomonal agent. Patients who had been exposed to previous therapy including an antipseudomonal agent were marginally more likely to have experienced a *P. aeruginosa* bloodstream infection with a strain resistant to ⩾1 of the study antibiotics than patient who had not been previously exposed (OR, 1.8; 95% CI, 1.0–3.4; $P = .06$; table 1). Previous exposure to a monotherapy was marginally associated with an increased risk of resistance (OR, 1.8; 95% CI, 0.92–3.6; $P = .07$). No statistically significant association was found between a previous combination therapy and risk of resistance (OR, 1.8; 95% CI, 0.35–7.8; $P = .47$). Bacteremia experienced between 1993 and 1998, hospitalization on other units than the acute-care medical services, urinary source of infection, septic shock as clinical mode of presentation ($P = .06$), and having experienced an invasive procedure (except a drainage tube) were other factors significantly associated with resistance to ⩾1 antibiotic.

Crude risk of resistance to an antibiotic after exposure to that same antibiotic. In univariate analysis, we did not attempt to distinguish between situations where an antibiotic had been received as a monotherapy or as part of a combination therapy (too few patients had received any specific antibiotic as part of a combination therapy). Previous exposure to ceftazidime was significantly associated with an increased risk of resistance of the bacteremic isolate toward this antibiotic (OR, 11.4; 95% CI, 1.6–64.7; $P = .008$; table 2). Similarly, previous treatment with imipenem was significantly associated with an increased risk of resistance toward itself (OR, 2.7; 95% CI, 1.1–6.5; $P = .02$), and previous exposure to piperacillin was marginally associated with an increased risk of resistance (OR, 4.4; 95% CI, 0.67–22.1; $P = .06$). In contrast, previous exposure to ciprofloxacin or an aminoglycoside was not associated with an increased risk of resistance to themselves.

Table 2. Univariate analysis of therapies, including ceftazidime, piperacillin, imipenem, ciprofloxacin, and aminoglycosides, as risk factors for antibiotic-specific resistance in 267 bacteremic strains of *Pseudomonas aeruginosa*.

Antipseudomonal agent, included in previous therapy	Resistance of the bacteremic strain to this agent		OR (95% CI)	*P*
	Yes (cases)	No (controls)		
Ceftazidime				
Yes	3	5	—	
No	13	246	11.4 (1.6–64.7)	.008
Piperacillin[a]				
Yes	3	6	—	
No	26	231	4.4 (0.67–22.1)	.06
Imipenem[a]				
Yes	11	25	—	
No	30	186	2.7 (1.1–6.5)	.02
Ciprofloxacin				
Yes	0	9	—	
No	15	243	0.0 (0.0–9.1)	1.0
Aminoglycoside				
Yes	6	26	—	
No	37	198	1.2 (0.39–3.4)	.61

[a] One isolate was not tested against piperacillin, and 15 were not tested against imipenem.

Average adjusted risk of resistance to an antibiotic after exposure to that same antibiotic. In multivariate analysis stratified for antipseudomonal agents, previous monotherapy with an antipseudomonal antibiotic was independently associated with an increased risk of subsequent resistance of the bacteremic strain to that antibiotic (OR, 2.5; 95% CI, 1.3–4.8; $P = .006$; table 3). The risk of subsequent resistance was not significantly increased among patients who had received a combination therapy (OR, 1.8; 95% CI, 0.55–5.6; $P = .34$). However, no significant difference was observed between combination therapies and monotherapies in terms of independent risk of subsequent resistance (OR, 0.70; 95% CI, 0.20–2.53; $P = .59$). Finally, severe sepsis or shock as the primary manifestation of bacteremia was marginally associated with an increased risk of resistance after controlling for previous antibiotic therapy.

DISCUSSION

For clinicians who initiate empiric treatment in a clinical situation compatible with *P. aeruginosa* bacteremia, it is crucial to assess the potential risk of a resistant causative bacterium. In this retrospective study, 80 (30%) of 267 consecutive bacteremic isolates of *P. aeruginosa* were resistant to ⩾1 antipseudomonal drug. Twenty-four percent of bacteremic episodes occurred in patients who had been previously exposed to one or several of these agents. Imipenem and aminoglycosides were the most commonly administered antibiotics before the bacteremic event, and they were also the agents toward which the bacteremic isolates were the most frequently resistant. In univariate analysis, previous exposure to ceftazidime, piperacillin, and imipenem were significantly or marginally associated with an increased risk of resistance of the bacteremic isolate to themselves. After controlling for covariates, the average resistance of the bacteremic strain to an antibiotic was 2.5 times more likely when the patient had received previous monotherapy with this antibiotic that when he had not been exposed to it. No other treatment variable and none of the characteristics related to patients and hospital environment independently predicted resistance of the bacteremic isolate to an antipseudomonal drug.

Exposure to antibiotics predisposes patients to colonization with *P. aeruginosa* intrinsically resistant to these agents. *P. aeruginosa* has also the capacity to rapidly become resistant during the course of an antipseudomonal drug treatment [10]. Therefore, previous therapies increase the risk of infections with selected resistant *P. aeruginosa* isolates [7]. Moreover, through the selection of resistant strains, previous exposure to antibiotics also increases the risk for the subsequent administration of an inadequate antimicrobial treatment [11]. Finally, inadequate antibiotic treatments of *P. aeruginosa* bloodstream infections significantly increase the case-fatality rate [7, 11–13], prolong the hospital stay, and generate higher general costs [3, 14].

In this study, aminoglycosides were frequently administered before the bacteremic event, and resistance toward these agents was common among the bacteremic isolates. Nevertheless, previous exposure to aminoglycosides was not associated with an increased risk of resistance. A possible explanation for this finding is that resistance toward aminoglycosides in these patients might not be due to a mechanism involving exposure to this antimicrobial class, but rather to the induction of the MexXY-OprM efflux system [15] by the exposure to other drugs. This multidrug efflux system of *P. aeruginosa* is responsible for resistance to aminoglycosides and is not only induced by exposure to aminoglycosides, but also by exposure to other classes of antibiotics such as macrolides or tetracycline [16].

The antibiotic ranking for postexposure risk of resistance differed in this study and that of Carmeli et al. [10]. In the latter work, exposure to imipenem was associated with the highest risk of resistance and ceftazidime with the lowest—findings the opposite of ours. Different study populations could explain these differences. Indeed, the study of Carmeli et al. [10] focused not only on bacteremic strains, but on both colonizing and invasive isolates from various clinical sites. In addition, patients included in the study by Carmeli et al. [10] were initially colonized with organisms susceptible to the antibiotics to which subsequent resistance was detected, and a minority of these resistant strains were proven to have emerged from the original susceptible clone. However, the study by Carmeli et al. [10] relied upon an even smaller number of resistant isolates than ours (28 vs. 81). One limitation of our work is the absence of genotyping of susceptible colonizing and resistant bacteremic strains, making it impossible to distinguish new acquisition of resistance by a previously susceptible strain from superinfection with a genetically unrelated resistant strain.

Considerable debate exists concerning the usefulness of combination therapies (usually the addition of an aminoglycosides to a β-lactam antibiotic) in order to reduce the risk of emergence of resistance in *P. aeruginosa* isolates [17–20]. In contrast to previous monotherapies, previous combination therapies did not predict subsequent resistance in this study. However neither us nor Carmeli et al. [10] found a significant difference in risk of resistance when monotherapy and combination therapies were directly compared with each other. We studied one of the largest retrospective series of *P. aeruginosa* bacteremia and had almost no missing information. Nevertheless, our study lacked power to identify differences in risk of resistance across antibiotics, as well as between monotherapy and combination therapies.

In conclusion, bacteremic events that followed exposure to antipseudomonal antibiotics were more likely to be due to resistant *P. aeruginosa* strains. Therefore, when initiating an empiric treatment for a possible *P. aeruginosa* bacteremia, clinicians should avoid previously administered antibiotics, and in

Table 3. Multivariate association, averaged across antipseudomonal agents, of previous exposure to an agent, and resistance to that same agent in 267 bacteremic strains of *Pseudomonas aeruginosa*.

Characteristic	Adjusted OR (95% CI)	*P*
Previous monotherapy with the agent	2.5 (1.3–4.8)	.006
Previous combination therapy including the agent	1.8 (0.55–5.6)	.34
Severe sepsis or septic shock	1.6 (0.94–2.6)	.08

NOTE. Stratified logistic regression analysis in which each episode of bacteremia contributed 5 times to the model (i.e., once per antipseudomonal agent). Variance estimates were adjusted for the resulting dependence among observations.

particular, they should avoid those that had been administered as monotherapies.

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Effectiveness of Combination Antimicrobial Therapy for *Pseudomonas aeruginosa* Bacteremia

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It remains controversial whether combination therapy, given empirically or as definitive treatment, for *Pseudomonas aeruginosa* bacteremia is associated with a better outcome than monotherapy. The aim of the present study was to compare the rates of survival among patients who received either combination therapy or monotherapy for *P. aeruginosa* bacteremia. We assembled a historical cohort of 115 episodes of *P. aeruginosa* bacteremia treated with empirical antipseudomonal therapy between 1988 and 1998. On the basis of susceptibility testing of the bacteremic *P. aeruginosa* isolate, we defined categories of empirical treatment, including adequate combination therapy, adequate monotherapy, and inadequate therapy, as well as corresponding categories of definitive therapy. Neither the adequacy of the empirical treatment nor the use of combination therapy predicted survival until receipt of the antibiogram. However, the risk of death from the date of receipt of the antibiogram to day 30 was higher for both adequate empirical monotherapy (adjusted hazard ratio [aHR], 3.7; 95% confidence interval [CI], 1.0 to 14.1) and inadequate empirical therapy (aHR, 5.0; 95% CI, 1.2 to 20.4) than for adequate empirical combination therapy. Compared to adequate definitive combination therapy, the risk of death at 30 days was also higher with inadequate definitive therapy (aHR, 2.6; 95% CI, 1.1 to 6.7) but not with adequate definitive monotherapy (aHR, 0.70; 95% CI, 0.30 to 1.7). In this retrospective analysis the use of adequate combination antimicrobial therapy as empirical treatment until receipt of the antibiogram was associated with a better rate of survival at 30 days than the use of monotherapy. However, adequate combination antimicrobial therapy given as definitive treatment for *P. aeruginosa* bacteremia did not improve the rate of survival compared to that from the provision of adequate definitive monotherapy.

Pseudomonas aeruginosa bacteremia occurs most frequently in critically ill patients, particularly those who are immunocompromised, have cancer, or are mechanically ventilated (14, 15, 32, 38). In these patients, bacteremia is often accompanied by symptoms of systemic inflammatory response syndrome (SIRS) (40). Despite recent advances in therapy, *P. aeruginosa* bacteremia remains fatal in more than 20% of cases (28). Over 50% of deaths occur within a few days (3, 13, 18). Therefore, prompt administration of adequate antipseudomonal treatment is essential (3, 24). Paradoxically, it has not been clearly established whether the adequacy of empirical antimicrobial therapy initiated for suspected *P. aeruginosa* bacteremia truly improves survival (3, 28, 30, 39). Initial treatment decisions are difficult to make because *P. aeruginosa* bacteremia is a presumptive diagnosis at first and little is known about the susceptibility of the causative agent until receipt of the antibiogram. No single antimicrobial regimen adequately covers all strains of *P. aeruginosa* (4, 7). Moreover, the value of combination therapy (a combination of a beta-lactam plus an aminoglycoside or one of these agents plus ciprofloxacin) compared to that of monotherapy remains controversial (9, 10, 12, 16, 22, 29, 37, 39).

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We report here on analyses of a retrospective cohort of 115 patients who received empirical therapy for *P. aeruginosa* bacteremia. The patients were monitored from day 1 of documented bacteremia through day 30. The study aims were threefold: (i) to determine whether adequate empirical combination therapy was associated with a lower rate of mortality during early follow-up (from the day of documented bacteremia to the day of receipt of the antibiogram), (ii) whether both empirical and definitive treatments independently predicted survival during late follow-up (from the time of receipt of the antibiogram to day 30 postbacteremia) among patients who were still alive at the time of receipt of the antibiogram, and (iii) whether combination antipseudomonal therapy was superior to monotherapy.

MATERIALS AND METHODS

Study population. The study was performed at the Geneva University Hospital, a 1,000-bed urban tertiary-care center in Geneva, Switzerland. The clinical microbiology laboratory database was searched to identify all patients with a positive blood culture for *P. aeruginosa* from 1 November 1988 to 30 November 1998. Hospital charts were reviewed to further identify patients who presented with symptoms of SIRS at the time of their bacteremia and who had received an empirical antimicrobial therapy that included at least one antipseudomonal agent; no hospital chart was missing. Other data were collected from the same sources. Because of the rather small sample size, multiple entries in the study were permitted when two independent episodes of *P. aeruginosa* bacteremia occurred in the same patient. The criteria used to designate an independent episode of *P. aeruginosa* bacteremia included a documented positive culture for the pathogen, no antecedent of inadequately treated *P. aeruginosa* bloodstream infection, and no positive blood culture for at least 30 days after completion of adequate antimicrobial therapy for a previous episode of *P. aeruginosa* bacteremia.

Dependent variables. The time to death from all causes was used as the primary outcome of interest to avoid potentially arbitrary distinctions between deaths related and unrelated to bacteremia episodes.

Categories of antimicrobial treatment. Empirical antipseudomonal therapy was defined as treatment that included at least one antipseudomonal agent and that was started no later than 24 h after the index positive blood sample for culture had been drawn. Definitive antipseudomonal therapy was defined as treatment that included at least one antipseudomonal agent and that was continued or commenced on the day that the antibiogram results were reported to the clinicians. Analyses were based on an intention-to-treat approach; switching or stopping of the antipseudomonal treatment at any other time during the course of follow-up was not taken into account. We limited our analyses to treatments received on the days that the first positive blood sample was drawn and the results of the antibiogram were received because we lacked information on why antimicrobial therapy was instituted, modified, or stopped at any other time during the follow-up. The lack of an ability to appropriately control for factors that motivate treatment change can result in strong residual confounding by indication (21). Monotherapy consisted of treatment with one of the following antipseudomonal antimicrobials: piperacillin, ceftazidime, imipenem, cefepime, or ciprofloxacin. Piperacillin-tazobactam was used infrequently and was grouped with piperacillin. Combination therapy consisted of the administration of piperacillin, ceftazidime, imipenem, or cefepime together with either an aminoglycoside (gentamicin or amikacin) or ciprofloxacin or the administration of an aminoglycoside together with ciprofloxacin. Antimicrobial therapy was considered adequate when the index bacteremic *P. aeruginosa* isolate was susceptible to the antimicrobial prescribed and the dose and pattern of administration were in accordance with current medical standards (piperacillin, 3 to 4 g every 4 h [q4h] to q6 h; ceftazidime, 2 g q8h; imipenem, 0.5 g q6h; cefepime, 2 g q12h; ciprofloxacin, 0.4 g intravenously q12h or 0.75 g orally q12h; gentamicin, a load of 2 mg/kg of body weight and then 1.7 mg/kg q8h or 5.1 mg/kg q24h). Combination therapy was considered adequate if the index bacteremic strain was susceptible to both drugs. The following antipseudomonal therapies were classified as inadequate: monotherapy with an agent to which the bacteremic *P. aeruginosa* strain was resistant, combination therapy with two agents to which the strain was resistant, and combination therapy with an aminoglycoside in association with another antipseudomonal agent to which the strain was resistant. In our institution gentamicin is not prescribed at doses exceeding 5.1 mg/kg per day. At this standard dose, gentamicin monotherapy has been associated with poor outcomes in patients with *P. aeruginosa* bacteremia (3, 9, 28). For this reason, in accordance with the findings of other investigators (37), gentamicin is not accepted as monotherapy for *P. aeruginosa* bacteremia in our institution, and patients receiving empirical aminoglycoside monotherapy were therefore excluded from the analysis. Several studies have suggested that ciprofloxacin monotherapy might be effective for febrile neutropenic patients and empirical treatment of bacteremia; however, higher incidences of superinfections caused by gram-positive pathogens, as well as poor outcomes in the case of infections caused by resistant gram-negative pathogens, have limited its use (1, 25, 31, 33). In contrast, to our knowledge, no negative data concerning ciprofloxacin monotherapy for the treatment of bacteremia caused by susceptible gram-negative isolates are available (20). Other investigators have accepted ciprofloxacin monotherapy as an adequate alternative for the treatment *P. aeruginosa* bacteremia (28, 37). For these reasons we considered ciprofloxacin monotherapy as an adequate treatment option, as long as the *P. aeruginosa* isolate was susceptible.

Hence, we distinguished the following categories of treatment: adequate empirical combination therapy (AECT), adequate empirical monotherapy (AEMT), inadequate empirical therapy (IET), adequate definitive combination therapy (ADCT), adequate definitive monotherapy (ADMT), and inadequate definitive therapy (IDT).

Covariates. Other potential prognostic factors were assessed, including age, sex, calendar year of the patient episode (treated as a dichotomic variable [1993 to 1998 versus 1988 to 1992]), clinical mode of presentation, type of bacteremia (mono- or polymicrobial), hospital unit, underlying medical condition, initial neutropenia, steroid treatment, and primary site of infection.

Statistical analysis. Patients for whom the date of receipt of the antibiogram was missing were excluded from analysis. Statistical analyses were done with the STATA program (version 6.0). Categorical variables were compared by Fisher's exact tests. The Kruskal-Wallis test was used to compare the time to receipt of the antibiogram across treatment groups. All statistical tests were two tailed.

(i) Survival over entire follow-up. We used the Kaplan-Meier product-limit method to estimate by univariate analysis the risk of death by empirical treatment categories. The reference time for this preliminary analysis was the day of the index positive blood culture. Patients were monitored until day 30 postbacteremia or were censored from analysis (because of either death or transfer to another hospital). The log-rank test was used to compare the cumulative probability of death across treatment groups.

(ii) Early follow-up. Early follow-up started on the date of bacteremia and extended to the end of the last day before receipt of the antibiogram. Contingency tables were used to compare baseline patient characteristics across empirical treatment groups. We calculated Kaplan-Meier estimates of the cumulative risk of death by patient characteristics. The corresponding unadjusted and multivariate-adjusted hazard ratios of death were estimated by Cox proportional hazard regression analysis. Treatment variables were always entered and retained in the multivariate models. Covariates were considered for inclusion if they were associated with survival with a P value of <0.20 by univariate analysis. To limit overfitting (11), only important confounding factors (i.e., variables whose inclusion or exclusion changed regression coefficients of treatments variables by $>10\%$) were retained in the model; no interaction term was examined.

(iii) Late follow-up. Analyses similar to those described above were performed for late follow-up, which started on the day of receipt of the antibiogram and extended to the end of day 30 postbacteremia. Analyses were restricted to patients who were still alive and who were monitored at the time that the antibiogram was received. Contingency tables assessed the patients' characteristics at the time of bacteremia by definitive treatment groups.

Detailed treatment history. To better define relations between survival and specified categories of therapies, we identified modifications of empirical therapies before receipt of the antibiogram, as well as changes in definitive therapies occurring after receipt of the antibiogram. In this analysis, discontinuation following treatment completion was not considered a modification of therapy.

Definitions. Underlying diseases were considered if they were present at the time of bacteremia and were defined clinically, analytically, hematologically, or histologically by use of standard criteria (17). Sepsis, severe sepsis, and shock were defined as described previously (40). Neutropenia was defined as a granulocyte count of less than 0.50×10^9/liter (6). Steroid therapy was considered notable if the patient had been receiving at least 30 mg of prednisone daily for at least 10 days before the bacteremia. Definitions of the source of bacteremia were as described elsewhere (2). The day of antibiogram receipt was defined as the day when the clinical microbiology laboratory notified the clinician that the antibiogram had been completed. In our internal experience, the delay between the sending of the report and its physical receipt by the clinicians did not exceed 6 h. Antimicrobial susceptibility was determined by disk diffusion methods according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) (36). An isolate was considered susceptible, intermediate, or resistant according to the criteria of the NCCLS. The isolates with intermediate susceptibility were classified as resistant for analysis.

RESULTS

Baseline characteristics. We identified 120 culture-proven episodes of *P. aeruginosa* bacteremia treated empirically with at least one antipseudomonal agent during the study period. Five (4.2%) episodes were excluded because of a missing date of receipt of the antibiogram or missing data on empirical treatment. Analyses were restricted to 115 episodes of *P. aeruginosa* bacteremia in 113 patients. Two patients experienced a second episode of bacteremia after completion of an adequate antipseudomonal therapy and intervals of 30 and 54 days, respectively. Exclusion of these episodes had virtually no effects on the overall results. For ease of presentation, we use the terms episode and patient interchangeably.

About half of the 115 patients were aged 65 years or older; most were men (Table 1). Half of the bacteremia episodes occurred between 1993 and 1998. A majority of patients were hospitalized on the medical ward or surgical intensive care unit; 19% presented with shock and 12% presented with severe sepsis. Eighty percent of the episodes were monobacterial. The most commonly identified sources of *P. aeruginosa* infection were the respiratory and urinary tracts. About 90% of patients had an underlying disease; 30% were neutropenic; 10% were receiving a steroid treatment. At one time or another during follow-up, 33 patients (28.7%) received imipenem, 22 (19.1%)

TABLE 1. Baseline characteristics of 115 *P. aeruginosa* bacteremic episodes empirically treated with an antipseudomonal antimicrobial regimen[a]

Variable	No. (%) of episodes
Sex (men)	85 (73.9)
Calendar time (1993 to 1998)	56 (48.7)
Hospital unit	
Medical	55 (47.8)
Surgical	20 (17.4)
Medical intensive care	16 (13.9)
Surgical intensive care	24 (20.9)
Clinical presentation	
Simple sepsis	79 (68.7)
Severe sepsis	14 (12.2)
Septic shock	22 (19.1)
Monobacterial bacteremia	92 (80.0)
Primary site(s) of *P. aeruginosa* infection	
Respiratory tract	24 (20.9)
Urinary tract	22 (19.1)
Vascular system	5 (4.3)
Other	21 (18.3)
Unknown	57 (49.6)
Underlying medical condition	
Cancer	52 (15.2)
AIDS	6 (5.2)
Diabetes	9 (7.8)
Respiratory dysfunction	23 (20.0)
Renal failure	19 (16.5)
Other[b]	50 (43.5)
None of the above	15 (13.0)
Neutropenia	34 (29.6)
Steroid treatment	11 (9.6)
Bacteremic strain resistant to the following no. of antipseudomonal agents:	
0	75 (65.2)
1	19 (16.5)
≥2	21 (18.3)

[a] The median age was 65 years (age range, 6 to 91 years).
[b] Heart failure, pancreatitis, and severe nonpseudomonal infection.

received piperacillin, 22 (19.1%) received ceftazidime, 12 (10.4%) received cefepime, 56 (48.7%) received gentamicin, 16 (13.9%) received amikacin, and 27 (23.5%) received ciprofloxacin. Resistance to at least one antipseudomonal agent was documented for 35% of the *P. aeruginosa* blood isolates.

Entire follow-up. Complete follow-up was achieved for 114 participants (99%). One patient was transferred to another hospital on the third day of follow-up. Forty-three patients (37.4%) had received AECT, 55 (47.8%) had received AEMT, and 17 (14.8%) had received IET. Forty-five patients died within 30 days of bacteremia (cumulative risk, 39.4%; 95% confidence interval [CI], 31.1 to 49.0); 33 deaths (73.3%) were directly attributed to bacteremia. The unadjusted probabilities of surviving until day 30 were 72.1% (95% CI, 56.1 to 83.1) for the AECT group, 61.2% (95% CI, 47.0 to 72.7) for the AEMT group, and 29.4% (95% CI, 10.7 to 51.2) for the IET group (Fig. 1) (global test, $P = 0.01$).

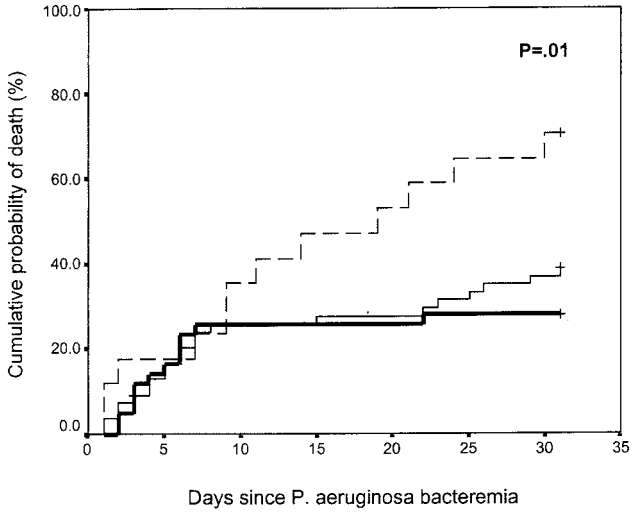

FIG. 1. Cumulative risk of death for patients who received adequate empirical combination therapy (bold solid line), adequate empirical monotherapy (narrow solid line), and inadequate empirical therapy (broken line).

Early follow-up. The median time from bacteremia to receipt of the antibiogram was 5 days (90th percentile, 7 days). The mean times until receipt of the antibiogram were 5.5 days for the IET group, 5.2 days for the AEMT group, and 5.1 days for the AECT group ($P = 0.60$). Most patients' baseline characteristics were similar across empirical treatment groups (Table 2). However, patients who had received AECT were significantly more likely to have had their bloodstream infection between 1988 and 1992 ($P = 0.001$). Sixteen patients died before the antibiogram was received (cumulative risk, 18.5%; 95% CI, 11.5 to 21.1). By univariate analysis there was no relation between empirical therapies and risk of death before receipt of the antibiogram (Table 2). By univariate analysis, the risk of death was significantly lower among patients over 64 years of age and among those whose bacteremia episode occurred after 1992. Higher risks were observed among patients who were hospitalized in the surgical intensive care unit, who presented with severe sepsis or shock, and who had bacteremia of respiratory origin.

By multivariate analysis, the risk of death before receipt of the antibiogram was also similar for the AEMT group (adjusted hazard ratio [aHR], 0.81; 95% CI, 0.31 to 2.1; $P = 0.66$) and the IET group (aHR, 1.2; 95% CI, 0.29 to 5.2; $P = 0.79$) compared to that for the AECT group (Table 3). Being older was independently associated with a lower risk of death (aHR, 0.22, 95% CI, 0.06 to 0.81; $P = 0.02$); having presented with severe sepsis (aHR, 31.5; 95% CI, 3.5 to 286; $P = 0.002$) and shock (aHR, 38.0; 95% CI, 5.4 to 268; $P < 0.001$) was associated with a higher risk.

Late follow-up. Of the 99 patients still alive and under follow-up at the time that the antibiogram was received, 1 was excluded from further analysis because of missing information on the definitive therapy. Of the 98 remaining patients, 46 (46.9%) had received ADCT, 33 (33.7%) had received ADMT, and 19 (19.4%) had received IDT (Table 4). Definitive treatment groups were similar with regard to most characteristics

TABLE 2. Baseline characteristics of study subjects in relation to categories of empirical antimicrobial therapy and summary of univariate survival analysis until receipt of the antibiogram[a]

Characteristic	% of episodes with:			No. who died/total no. (Kaplan-Meier %)[b]	Univariate HR (95% CI)	*P* value
	Adequate combination therapy (n = 43)	Adequate monotherapy (n = 55)	Inadequate therapy (n = 17)			
All patients	100.0	100.0	100.0	16/115 (18.5)		
Empirical antimicrobial therapy						
Adequate combination therapy	100.0	0.0	0.0	7/43 (29.7)	1.0 (referent)	
Adequate monotherapy	0.0	100.0	0.0	6/55 (11.1)	0.67 (0.23–1.9)	0.46
Inadequate therapy	0.0	0.0	100.0	3/17 (17.7)	1.1 (0.29–4.5)	0.86
Age (yr)						
<65	41.2	49.1	51.2	13/56 (34.7)	1.0 (referent)	
≥65	58.8	50.9	48.8	3/59 (5.1)	0.20 (0.06–0.69)	0.01
Calendar time						
1988 to 1992	69.8	47.3	17.6	9/39 (36.4)	1.0 (referent)	
1993 to 1998	30.2	52.7	82.4	7/76 (9.5)	0.38 (0.14–1.0)	0.05
Hospitalized on surgical intensive care unit						
No	83.7	80.0	64.7	9/91 (13.2)	1.0 (referent)	
Yes	16.3	20.0	35.3	7/24 (35.7)	3.2 (1.2–8.5)	0.02
Clinical presentation						
Simple sepsis	67.4	69.1	70.6	1/79 (1.3)	1.0 (referent)	
Severe sepsis	18.6	10.9	0.0	7/14 (42.9)	28.1 (3.4–229.9)	0.002
Shock	14.0	20.0	29.4	10/22 (56.3)	45.5 (5.9–348.3)	<0.001
Type of bacteremia						
Pseudomonas alone	74.4	85.5	76.5	12/92 (20.9)	1.0 (referent)	
Poymicrobial	25.6	14.5	23.5	4/23 (17.4)	0.88 (0.27–2.8)	0.83
Underlying medical condition(s)[c]						
No	14.0	14.5	5.9	2/15 (13.3)	1.0 (referent)	
Yes	86.0	85.5	94.1	14/100 (19.6)	1.8 (0.22–14.6)	0.58
Immunological risk factor(s)						
None of the following	55.8	67.3	70.6	7/73 (12.2)	1.0 (referent)	
Neutropenia	39.5	25.5	17.6	6/34 (18.3)	2.0 (0.68–5.8)	0.21
Steroid treatment	7.0	10.9	11.8	3/11 (59.1)	3.4 (0.95–12.0)	0.06
Neutropenia and/or steroid treatment	44.2	32.7	29.4	9/42 (33.4)	2.6 (0.96–7.0)	0.06
Primary site(s) of infection						
Unknown	51.2	52.7	35.3	7/57 (13.0)	1.0 (referent)	
Respiratory tract	20.9	16.4	35.3	8/24 (55.0)	2.9 (1.1–7.5)	0.03
Urinary tract	20.9	20.0	11.8	0/22 (0.0)	0.0 (ND[d])	ND
Vascular system	4.7	5.5	0.0	0/5 (0.0)	0.0 (ND)	ND
Other	20.9	14.5	23.5	3/21 (14.3)	1.2 (0.30–4.4)	0.83

[a] Seven episodes of bacteremia were excluded from this analysis either because of missing empirical treatment (n = 2) or missing dates of receipt of the antibiogram (n = 5).
[b] Kaplan-Meier product limit estimate of cumulative risk of death from all causes.
[c] Cancer, AIDS, diabetes, respiratory dysfunction, renal failure, heart failure, pancreatitis, and/or severe nonpseudomonal infection.
[d] ND, not defined.

recorded at the time of bacteremia. However, definitive antimicrobial therapy of a particular type (i.e., adequate combination therapy, adequate monotherapy, or inadequate therapy) was significantly more likely to have followed an empirical treatment of the same type ($P < 0.001$). Twenty-nine patients died before the end of follow-up (cumulative risk, 32.4%; 95% CI, 23.3 to 43.9).

In contrast to the risk of death during early follow-up, the risk of death after receipt of the antibiogram varied according to empirical therapy. By univariate analysis, the risk of death was significantly higher for the IET group (crude hazard ratio [cHR], 6.8; 95% CI, 2.3 to 20.3) and marginally higher for the AEMT group (cHR, 2.5, 95% CI, 0.88 to 6.9) than for the AECT group (Table 4). The multivariate Cox proportional hazard model was stratified on severe sepsis and shock to limit violation of the proportional hazard assumption. After further controlling for independent prognostic factors and definitive treatment, patients in the AEMT group were 3.7 times more

TABLE 3. Results of a Cox proportional hazard model describing independent relations between empirical antimicrobial therapy and risk of death during early follow-up[a]

Characteristic	Hazard ratio	95% CI	*P* value
Empirical antimicrobial therapy			
Adequate combination therapy	1.0		
Adequate monotherapy	0.81	0.31–2.1	0.66
Inadequate therapy	1.2	0.29–5.2	0.79
Age (yr)			
<65	1.0		
≥65	0.22	0.06–0.81	0.02
Clinical presentation			
Simple sepsis	1.0		
Severe sepsis	31.5	3.5–286.4	0.002
Shock	38.0	5.4–267.8	<0.001

[a] Early follow-up started on the date of bacteremia and extended to the end of the last day before receipt of the antibiogram. Similar results were obtained after exclusion of the 26 patients who had a known urinary or vascular source of *P. aeruginosa* infection.

likely (95% CI, 1.0 to 14.1; $P = 0.05$) and patients in the IET group were 5.0 times more likely (95% CI, 1.2 to 20.4; $P = 0.02$) to have died during late follow-up than patients in the AECT group (Table 5). There was no independent difference in the risk of death between patients in the IET and AEMT groups (aHR, 1.3; 95% CI, 0.54 to 3.3; $P = 0.52$).

Adequate definitive therapies were associated with better outcomes, but there was no evidence for the superiority of combination therapy over monotherapy. By univariate analysis, the risk of death for the ADMT group (cHR, 1.2; 95% CI, 0.50 to 2.9) was similar to that for the ADCT group, but the risk of death was significantly higher for the IDT group (cHR, 3.6, 95% CI, 1.4 to 8.9) than for the ADCT group (Table 4). Hospitalization on the surgical intensive care unit and severe sepsis or shock at the time of bacteremia were significant predictors of poor survival. There was a trend for bacteremia of urinary and vascular origin to be associated with a better prognosis. By multivariate analysis, the risk of death was significantly higher for the IDT group (aHR, 2.6; 95% CI, 1.1 to 6.7; $P = 0.04$) but not for the ADMT group (aHR, 0.70; 95% CI, 0.30 to 1.7; $P = 0.42$) compared to that for the ADCT group (Table 5). Hospitalization on the surgical intensive care unit was independently associated with poor survival (aHR, 3.2; 95% CI, 1.2 to 8.9; $P = 0.02$), and bacteremia of urinary or vascular origin was associated with better survival (aHR, 0.21; 95 CI, 0.05 to 0.94; $P = 0.04$).

Details on treatment changes during follow-up. Empirical treatment was unmodified until receipt of the antibiogram (or death for those who died during early follow-up) in 80 of 115 patients (Table 6). A switch of therapy during early follow-up was recorded for 18.6% of patients in the AECT group, 38.2% of those in the AEMT group (relative risk [RR], 2.1; 95% CI, 1.0 to 4.2; $P = 0.05$), and 35.3% of those in the IET group (RR, 1.9; 95% CI, 0.77 to 4.7; $P = 0.19$) (Table 6). No adequate empirical combination therapy was modified on the day of receipt of the antibiogram, while three AEMTs (8.8%) were replaced by an ADCT and one IET (4.8%) was replaced by an ADMT. Finally, 13 definitive treatments were modified before the end of follow-up or death: 5 of these changes (38.5%) consisted of downgrading of an ADCT to an ADMT, while 3 (23.0%) consisted of upgrading of an ADMT to an ADCT, and 5 (38.5%) consisted of upgrading of an IDT to either an ADMT or an ADCT.

Monotherapy subanalysis. The adequacies of both aminoglycoside monotherapy and ciprofloxacin monotherapy for *P. aeruginosa* bacteremia are controversial. Therefore, we conducted complementary univariate analyses to describe the risk of death among patients treated with aminoglycoside or ciprofloxacin monotherapy and examined the impact of alternative definitions of monotherapy adequacy on the results of multivariate analysis. The crude cumulative risk of death during follow-up was 35.0% (95% CI, 18.5 to 59.7%) for 20 patients who received an active aminoglycoside monotherapy empirically. The crude cumulative risks of death were 25% (95% CI, 11.3 to 50.0%) before receipt of the antibiogram and 15.2% (95% CI, 4.0 to 48.8%) after receipt of the antibiogram. Among 12 patients who received active ciprofloxacin monotherapy empirically, the crude cumulative risks of death were 33.3% (95% CI, 14.0 to 66.3%) over the entire follow-up, 0% before receipt of the antibiogram, and 34.4% (95% CI, 14.4 to 68.0%) after receipt of the antibiogram. The crude risk of death before receipt of the antibiogram was marginally higher among patients who received empirical aminoglycoside monotherapy than among patients who received empirical ciprofloxacin monotherapy ($P = 0.07$; HR was undefined). There was a trend in the opposite direction for the risk of death after receipt of the antibiogram (cHR, 0.21; 95% CI, 0.11 to 1.9; $P = 0.16$). In our main analysis sections, to reflect the consensus that has been achieved in our institution, we excluded patients who received empirical combination therapy with an active aminoglycoside associated with a nonantipseudomonal agent and included in the inadequate therapy groups patients who received an active aminoglycoside in combination with an inactive antipseudomonal agent. In contrast, we included in the adequate monotherapy groups patients who received active ciprofloxacin in combination with either a nonantipseudomonal agent or an inactive antipseudomonal agent. As a complement, we conducted two additional multivariate analyses. In the first one, monotherapy with an active aminoglycoside and monotherapy with active ciprofloxacin were both considered adequate; in the second one, neither regimen was considered adequate. Both analyses confirmed that inadequate empirical and definitive therapies were associated with poor outcomes; both analyses also supported the notion that the type of empirical therapy is not an independent predictor of death before receipt of the antibiogram (data not shown). Moreover, the aHRs at 30 days for patients in the AEMT group compared to that for patients in the AECT group were 2.0 in the first analysis (95% CI, 0.67 to 6.2) and 2.3 in the second analysis (95% CI, 0.62 to 8.7). Although neither result was statistically significant, both concur with the findings of the main multivariate analyses in suggesting that adequate empirical combination therapy was associated with better outcomes at day 30 than adequate empirical monotherapy.

TABLE 4. Baseline characteristics of study subjects in relation to categories of definitive antipseudomonal therapy and summary of univariate survival analysis from receipt of the antibiogram to end of follow-up for 98 patients[a]

Characteristic	% of episodes with:			No. who died/total no. (Kaplan-Meier %)[b]	Univariate HR (95% CI)	*P* value
	Adequate combination therapy (n = 46)	Adequate monotherapy (n = 33)	Inadequate therapy (n = 19)			
All patients	100.0	100.0	100.0	29/98 (32.4)		
Empirical antimicrobial therapy						
Adequate combination therapy	58.7	12.1	26.3	5/36 (16.0)	1.0 (referent)	
Adequate monotherapy	30.4	81.8	42.1	15/49 (33.9)	2.5 (0.88–6.9)	0.09
Inadequate therapy	10.9	6.1	31.6	9/13 (71.2)	6.8 (2.3–20.3)	0.001
Adequate monotherapy or inadequate therapy	41.3	87.9	73.7	24/62 (42.1)	3.2 (1.2–8.4)	0.02
Definitive antimicrobial therapy						
Adequate combination therapy	100.0	0.0	0.0	10/46 (21.7)	1.0 (referent)	
Adequate monotherapy	0.0	100.0	0.0	9/33 (32.5)	1.2 (0.50–2.9)	0.68
Inadequate therapy	0.0	0.0	100.0	10/19 (57.9)	3.6 (1.4–8.9)	0.006
Adequate monotherapy or inadequate therapy	0.0	100.0	100.0	19/52 (42.2)	1.8 (0.86–4.0)	0.12
Age (yr)						
<65	47.8	39.4	42.1	11/43 (28.8)	1.0 (referent)	
≥65	52.2	60.6	57.9	18/55 (35.4)	1.3 (0.60–2.7)	0.54
Calendar time						
1988 to 1992	50.0	45.5	36.8	8/30 (31.1)	1.0 (referent)	
1993 to 1998	50.0	54.5	63.2	21/68 (33.1)	1.1 (0.51–2.6)	0.74
Hospitalized on surgical intensive care unit						
No	78.3	84.8	89.5	20/81 (28.0)	1.0 (referent)	
Yes	21.7	15.2	10.5	9/17 (52.9)	2.9 (1.3–6.6)	0.009
Clinical presentation						
Simple sepsis	76.1	78.8	84.2	17/77 (24.1)	1.0 (referent)	
Severe sepsis	8.7	9.1	10.5	4/8 (100.0)	2.6 (1.0–6.7)	0.05
Shock	15.2	12.1	5.3	8/13 (61.5)	4.1 (1.7–9.8)	0.002
Type of bacteremia						
Pseudomonas alone	78.3	87.9	78.9	24/80 (32.3)	1.0 (referent)	
Poymicrobial	21.7	12.1	21.1	5/18 (30.2)	1.0 (0.42–2.6)	0.95
Underlying medical condition(s)[c]						
No	10.9	21.2	5.3	2/13 (16.1)	1.0 (referent)	
Yes	89.1	78.8	94.7	27/85 (34.8)	2.3 (0.56–9.1)	0.25
Immunological risk factor(s)						
None of the following	60.5	81.3	72.2	18/65 (30.4)	1.0 (referent)	
Neutropenia	39.5	18.8	27.8	8/28 (31.8)	1.1 (0.47–2.5)	0.87
Steroid treatment	13.3	7.1	13.3	4/8 (50.0)	2.0 (0.69–5.8)	0.20
Primary site(s) of infection						
Unknown	47.8	45.5	68.4	15/50 (33.4)	1.0 (referent)	
Respiratory tract	17.4	15.2	15.8	7/16 (44.4)	1.5 (0.63–3.6)	0.35
Urinary tract	17.4	33.3	10.5	3.21 (19.6)	0.39 (0.12–1.2)	0.11
Vascular system	8.7	3.0	0.0	0/5 (0.0)	0.0 (ND[d])	ND
Other	26.1	9.1	15.8	6/18 (33.3)	1.1 (0.41–2.8)	0.89
Time between bacteremia and receipt of antibiogram (days)						
<5	52.2	51.5	31.6	16/47 (34.0)	1.0 (referent)	
≥5	47.8	48.5	68.4	13/51 (25.7)	0.89 (0.42–1.9)	0.75

[a] One additional patient was excluded from this analysis because of missing definitive treatment.
[b] Kaplan-Meier product limit estimate of cumulative risk of death from all causes.
[c] Cancer, AIDS, diabetes, respiratory dysfunction, renal failure, heart failure, pancreatitis, and/or severe nonpseudomonal infection.
[d] ND, not defined.

TABLE 5. Results of a stratified Cox proportional hazard model describing independent relations between both empirical and definitive antimicrobial therapy and risk of death during late follow-up[a]

Characteristic	Hazard ratio	95% CI	*P* value
Empirical antimicrobial therapy			
Adequate combination therapy	1.0		
Adequate monotherapy	3.7	1.0–14.1	0.05
Inadequate therapy	5.0	1.2–20.4	0.02
Definitive antimicrobial therapy			
Adequate combination therapy	1.0		
Adequate monotherapy	0.70	0.30–1.7	0.42
Inadequate therapy	2.6	1.1–6.7	0.04
Hospitalization on the surgical intensive care unit			
No	1.0		
Yes	3.2	1.2–8.9	0.02
Bacteremia of urinary or vascular origin			
No	1.0		
Yes	0.21	0.05–0.94	0.04

[a] The model was stratified on dummy variables coding for severe sepsis and shock to account for violations of the proportional hazard assumption. Late follow-up started on the day of receipt of the antibiogram and extended to the end of day 30 post bacteremia.

DISCUSSION

In our cohort of patients with *P. aeruginosa* bacteremia and SIRS, adequate empirical combination therapy was independently associated with better survival at 1 month compared to that achieved with adequate empirical monotherapy. In contrast, the rates of mortality prior to receipt of the antibiogram were similar among those who had received no, one, or two adequate antipseudomonal agents. Adequate definitive monotherapy and adequate definitive combination therapy were both independently associated with better survival outcome compared to survival achieved with inadequate definitive therapy.

Both the importance of an appropriate empirical therapy and the role of combination therapies for *P. aeruginosa* bacteremia are controversial. Unfortunately, cases of *P. aeruginosa* bacteremia have only rarely been included in randomized treatment trials. Indeed, in a review of 10 randomized trials of antimicrobial therapy in patients with cancer and neutropenia, only 90 of a total of 909 episodes of bacteremia were caused by *Pseudomonas* species, and there was no subgroup analysis of treatment efficacy by organism (16). Therefore, present guidelines rely mostly on observational studies. Inappropriate definitive therapy for *P. aeruginosa* bacteremia was a predictor of poor clinical outcome in most recently published observational studies (3, 9, 24, 28, 39), and the importance of the appropriateness of definitive treatment for *P. aeruginosa* bacteremia is therefore generally accepted. A delay in the administration of appropriate antimicrobial therapy has been associated with lower cure rates in some studies (3, 30); however, this was not confirmed by others (28, 39). Similarly, combination therapy was superior to monotherapy in one study (22), but not in others (3, 9, 28, 37, 39). A major shortcoming of previous observational studies is the possible bias due to the death of some patients before they matched the definition for a particular treatment category (e.g., therapy was received for at least 2 days) (22). Comparison between the available studies is also made difficult by different study designs. Some were prospective (22, 39), some excluded polymicrobial bacteremia (9, 28), some did not use overall survival as the main outcome (3, 9), and, most importantly, some did not account for the results of in vitro susceptibility testing in the definition of adequate therapy (3, 9). Moreover, monotherapy with an aminoglycoside, which nowadays is not accepted as an appropriate therapy for *P. aeruginosa* bacteremia unless high doses (7 mg/kg/day) are used, was considered appropriate in previous studies (3, 9, 28). In other studies, this issue was not addressed (22, 39), and it is therefore possible that the superiority of combination therapy over monotherapy resulted from the inclusion in the monotherapy group of patients who had been treated with standard doses of an aminoglycoside alone (22). Present guidelines for the treatment of suspected *P. aeruginosa* bacteremia recommend the rapid introduction of empirical antimicrobial therapy that includes at least one antipseudomonal agent. Some investigators, because of worry regarding initial resistance to the empirically chosen antipseudomonal agent, suggest the addition of an aminoglycoside for 3 to 5 days (10, 12). This is indeed a serious concern, as the prevalence of resistance of the invasive strain to antipseudomonal agents was higher in our cohort than in older series (3, 22, 28). Empirical combination therapy could also reduce the risk of selection of resistant clones during initial therapy (5, 7, 26, 34, 35). This is supported by our recent findings suggesting differences in the susceptibility patterns of bacteremia-causing *P. aeruginosa* isolates previously exposed to monotherapies and combination therapies (4). The emergence of antimicrobial resistance during therapy for *P. aeruginosa* bacteremia is difficult to detect and may lead to inappropriate definitive therapy, with increased rates of mortality and prolonged hospital stays (8, 24, 27). Moreover, greater killing might be achieved by combination therapies acting synergistically; this might be of particular importance early during the infectious process, when a rapid reduction of the pathogen burden might prevent the evolution toward sepsis. One concern with combination therapies is the risk of nephrotoxicity or ototoxicity when aminoglycosides are used (12). It is therefore recommended that aminoglycosides be given only for a short time (3 to 5 days) (10, 12). This approach is supported by the present study, which suggests that empirical combination therapy increases survival at 30 days, even if it is given for only 3 to 5 days and is followed by monotherapy.

Why does empirical therapy not influence mortality until receipt of the antibiogram? One reasonable hypothesis is that some patients are so sick that they will die within the first days following *P. aeruginosa* bacteremia, independently of any antimicrobial therapy. In contrast, patients in better clinical condition at the time of *P. aeruginosa* bacteremia might survive a few days independently of the appropriateness of antimicrobial treatment. Evidence supporting this hypothesis comes from the observation that clinical presentation at the onset of bacteremia is the strongest independent indicator of survival.

Like others (39), we observed that inadequate empirical antimicrobial therapies had sometimes not been modified according to the antibiogram results. It is likely that favorable

TABLE 6. Modifications of antimicrobial therapy within 30 days postbacteremia

Treatment type, time of modification	Modification	No. (%) of episodes
Empirical antimicrobial therapy, during early follow-up		
Adequate combination therapy (n = 43)	No modification	35 (81.4)
	Switch to adequate monotherapy	6 (14.0)
	Switch to inadequate therapy	2 (4.6)
Adequate monotherapy (n = 55)	No modification	34 (61.8)
	Switch to adequate combination therapy	12 (21.8)
	Switch to inadequate therapy	9 (16.4)
Inadequate therapy (n = 17)	No modification	11 (64.7)
	Switch to adequate combination therapy	5 (29.4)
	Switch to adequate monotherapy	1 (5.9)
Empirical antimicrobial therapy, at receipt of antibiogram[a]		
Adequate combination therapy (n = 43)	No modification	43 (100.0)
	Switch to adequate monotherapy	0 (0.0)
	Switch to inadequate therapy	0 (0.0)
Adequate monotherapy (n = 34)	No modification	31 (91.2)
	Switch to adequate combination therapy	3 (8.8)
	Switch to inadequate therapy	0 (0.0)
Inadequate therapy (n = 21)	No modification	20 (95.2)
	Switch to adequate combination therapy	0 (0.0)
	Switch to adequate monotherapy	1 (4.8)
Definitive antimicrobial therapy, during late follow-up[b]		
Adequate combination therapy (n = 46)	No modification	39 (92.0)
	Switch to adequate monotherapy	5 (8.0)
	Switch to inadequate therapy	0 (0.0)
Adequate monotherapy (n = 33)	No modification	30 (83.6)
	Switch to adequate combination therapy	3 (16.4)
	Switch to inadequate therapy	0 (0.0)
Inadequate therapy (n = 19)	No modification	11 (70.1)
	Switch to adequate combination therapy	1 (9.0)
	Switch to adequate monotherapy	4 (20.9)

[a] Sixteen patients died before receipt of the antibiogram; data on treatment modification between day 2 and the last day before receipt of the antibiogram were missing for one patient.

[b] Four patients died on the day of receipt of the antibiogram; data on treatment modifications after receipt of the antibiogram were missing for one patient.

evolution, despite treatment inadequacy, influenced the clinician's decisions in this sense. Older age was unexpectedly associated with better survival. However, our restrictive inclusion criteria (positive blood culture for *P. aeruginosa* in association with SIRS and administration of an empirical antimicrobial therapy that included at least one agent with antipseudomonal activity) probably selectively excluded from analysis elderly patients with poor prognoses. Indeed, blood samples for culture were probably less frequently obtained from elderly patients who had underlying conditions associated with a very poor prognosis. The elderly patients included in the analysis were also significantly more likely than younger patients to have characteristics associated with a better outcome (bacteremia of urinary origin, no neutropenia, and no steroid treatment).

Our study design was based on recommendations for high-quality observational studies for the evaluation of therapeutic effectiveness (19, 23). Nevertheless, we cannot exclude the possibility that estimates of treatment effects were biased by an imbalance associated with the therapeutic choices not accounted for in the multivariate analyses. This seems unlikely, because clinicians were uncertain about the diagnosis of *P. aeruginosa* bacteremia and unaware of the susceptibility to antimicrobials of the infecting strain at the time that they initiated empirical antimicrobial therapy. Because our sample size was small from a statistical viewpoint, multivariate analyses assessed only a limited number of therapy categories and controlled for only a few covariates simultaneously. Finally, analysis could not account for intercurrent treatment modifications which should have led to an attenuation of the observed differences in mortality across treatment groups.

We suggest that clinicians who suspect *P. aeruginosa* bacteremia initiate empirical therapy with two antipseudomonal agents. In the case of proven *P. aeruginosa* bacteremia, this combination therapy could be changed to monotherapy on the basis of the specific susceptibility pattern of the initial isolate. It is hoped that such an approach may reduce the risk of

selection of antimicrobial agent-resistant strains and avoid inadequate empirical therapies without increasing the risk of drug toxicity.

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CONCLUSION

P. aeruginosa is an increasingly prevalent opportunistic human pathogen, which is of special interest to the hospital physician. Amongst the numerous attributable infections it can produce, bacteremia is especially feared because of the high mortality and the difficulty to choose the appropriate antibiotic therapy.

This work was designed to study three important and controversial issues of *P. aeruginosa* bacteremia: (I) does preceding exposure to antibiotics increase the risk of resistance of the bacteremic strain ? (II) what is the influence of empirical and definitive treatment on survival ? and (III) does the use of a combination therapy as empirical and/or definite therapy improve the outcome ?

To address these questions we studied retrospectively all the *P. aeruginosa* bacteremias that occurred during a ten year period at the University Hospital of Geneva.

In the first article related to the influence of preceding antibiotic therapy on the susceptibility pattern of *P. aeruginosa* bacteremic isolates, the univariate analysis revealed that previous exposure to ceftazidime, piperacillin and imipenem were associated with an increased risk of resistance of the bacteremic isolates to themselves. The multivariate analysis showed a 2,5 time increase in the risk of resistance among the isolates of episodes of bacteremia which had been preceded by the exposure to an antibiotic as a monotherapy.

In the second article we analyzed the impact of combination versus monotherapy during both empirical and definite therapy for *P. aeruginosa* bacteremia on survival at the time the resistance profile of the bacteremic strain became available and at one month. We were unable to detect a relation between adequacy of the empirical therapy and the risk of death before reception of the antibiogram, mortality being influenced at that stage by age and clinical presentation. On the contrary, late outcome varied according to empirical and definitive therapy. Better survival at one month was independently associated with an adequate empirical combination therapy and with either an adequate definitive mono or combination antibiotherapy.

Together these findings led us to conclude that, when initiating an empiric treatment for a possible *P. aeruginosa* bacteremia, clinicians should avoid previously administered antibiotics especially if these have been given as monotherapy. We recommend the rapid introduction of a combination therapy while awaiting the result of the antibiogram. This combination therapy can be

safely switched to an adequate monotherapy based on the resistance profile of the bacteremic strain after 3 to 5 days

RESUME EN FRANCAIS

Pseudomonas aeruginosa représente la 3 ème cause de bactériémie à Gram-négatif et est associé à une mortalité de 25%.

Nous avons étudié la relation entre l'exposition préalable à certains antibiotiques antipseudomonaux et les résistances des souches bactériémiques. Le risque de résistance à la ceftazidime, à l'imipenem et à la pipéracilline augmente significativement. Les souches, dont l'épisode de bactériémie a été précédé par l'exposition à un antibiotique sous forme de monothérapie ont 2,5 fois plus de risque d'être résistantes à cet agent, comparé à son exposition en bithérapie.

Une bithérapie empirique adéquate, ainsi qu'une mono et bithérapie définitive adéquate sont associées à une meilleure survie des patients à un mois.

Lors de bactériémie à *P. aeruginosa*, nous recommandons d'introduire une bithérapie en évitant tout antibiotique ayant été employé avant l'épisode de bactériémie. Cette bithérapie pourra être remplacée ultérieurement par une monothérapie adéquate, basée sur l'antibiogramme de la souche bactériémique.