Intensive Care Med (2006) 32:1773–1781
DOI 10.1007/s00134-006-0354-8

ORIGINAL

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Outcome in bacteremia associated with nosocomial pneumonia and the impact of pathogen prediction by tracheal surveillance cultures

Received: 9 November 2005
Accepted: 27 July 2006
Published online: 16 September 2006

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Abstract *Objective:* To assess whether pathogen prediction in bacteremia associated with nosocomial pneumonia (NP) by tracheal surveillance cultures improves adequacy of early antibiotic therapy and impacts mortality. *Design and setting:* A retrospective observational study of a prospectively gathered cohort. This cohort included all adult patients admitted to the ICU of a tertiary care hospital from 1992 through 2001 and who developed bacteremia associated with NP. *Measurements and main results:* 128 episodes of bacteremia associated with NP were identified. In 110 episodes a tracheal surveillance culture 48–96 h prior to bacteremia was available: this culture predicted the pathogen in 67 episodes (61%). Overall rates of appropriate empiric antibiotic therapy within 24 and 48 h were 62 and 87%, respectively. Pathogen prediction was associated with a significantly higher rate of appropriate antibiotic therapy within 24 h (71 vs 45%; $p = 0.01$), but not within 48 h (91 vs 82%; $p = 0.15$). Crude in-hospital mortality was 50%. Pathogen prediction was associated with increased survival in univariate (OR 0.43; CI 0.19–0.93; $p = 0.04$) and multivariate analysis (OR 0.32; CI 0.12–0.82; $p = 0.02$). Multivariate analysis further identified age (OR 1.04; CI 1.01–1.07; $p = 0.02$), increasing APACHE II score (OR 1.08; CI 1.02–1.15; $p = 0.01$), and methicillin-resistant *Staphylococcus aureus* (OR 5.90; CI 1.36–25.36; $p = 0.01$) and *Pseudomonas aeruginosa* (OR 3.30; CI 1.04–10.4; $p = 0.04$) as independent risk factors for mortality. *Conclusion:* Pathogen prediction in bacteremia associated with NP by tracheal surveillance cultures is associated with a higher rate of adequate empiric antibiotic therapy within 24 h and with increased survival.

Keywords Nosocomial pneumonia · Bacteremia · Bacterial drug resistance · Surveillance cultures · *Pseudomonas aeruginosa* · Methicillin resistance · Mortality

Abbreviations *APACHE II:* acute physiology and chronic health evaluation II · *CAZ-R:* ceftazidime resistant Enterobacteriaceae · *CI:* confidence interval · *ESBL:* extended spectrum beta lactamase · *FiO_2:* fraction of inspired oxygen · *MDR:* multidrug resistant · *MSSA:* methicillin-sensitive *Staphylococcus aureus* · *MRSA:* methicillin-resistant *S. aureus* · *NF:* nonfermenting organism · *OR:* Odds ration · *PEEP:* positive end-expiratory pressure · *VAP:* ventilator-associated pneumonia

Introduction

Pneumonia is a leading cause of infection in the ICU, with invasive mechanical ventilation as the main risk factor [1, 2, 3, 4]. Mortality of nosocomial pneumonia depends on the degree of severity of illness at the time of diagnosis [5], on the causative microbial organism [6, 7, 8], and on the appropriateness of initial empiric antimicrobial therapy [9, 10, 11, 12]. Empiric choices must be optimized to balance the necessity to target the causative organism(s) against the drawbacks associated with overuse of broad-spectrum antibiotic therapy, such as an increased selection pressure for multidrug antibiotic resistance [13, 14]. As a possible solution to strike this balance, the concept of de-escalation therapy has emerged, consisting of initial administration of broad-spectrum empiric therapy for rapid adequate antimicrobial coverage, followed by streamlining and narrowing the spectrum when possible once etiology is known, in order to relieve subsequent selection pressure [15, 16, 17]. Anticipating the likely etiology of a newly developing infection from prior surveillance cultures alternatively could help to optimize empiric antibiotic choices.

At our ICU, an intensive surveillance system was set up in the late 1980s in order to control an outbreak of extended-spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae*. Since then, the surveillance protocol became common practice in the ICU and has been used as a tool in choosing empiric antibiotic therapy. In a previous paper, we reported that knowledge of colonization status prior to infection was associated with higher rates of appropriate therapy in patients with bacteremia caused by multidrug resistant (MDR) Gram-negative bacteria [18]. Recently, we have also shown that knowledge of colonization status added to adequacy of early antibiotic therapy in patients with bacteremia associated with nosocomial pneumonia (NP) and risk factors for MDR infection, although overall pathogen prediction by surveillance was only moderate [19]. In the present study, we wanted to examine whether in this population pathogen prediction influenced outcome and whether this outcome was determined by the type of MDR pathogen. The results of this study have been partially presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy [20].

Materials and methods

Setting and patients

The study was performed in the 54-bed, mixed medical-surgical ICU of the 1060-bed Ghent University Hospital. Generally, empiric use of carbapenems and glycopeptides is restricted to patients with known colonization with antibiotic resistant bacteria. Downgrading antibiotic therapy once microbial etiology is known is promoted. The need for continuing antimicrobial therapy is evaluated daily. Antibiotic therapy is weekly discussed in a multidisciplinary meeting of the attending ICU physician with the hospital infectious diseases specialist and microbiologist.

The case finding and study population were described previously [19]. In short, we did a retrospective cohort study of episodes of bacteremia associated with NP in an 11-year period (1992 through 2002). A laboratory-based surveillance of all positive blood cultures has been performed by the infection control team throughout the study period with registration of clinical significance, nosocomial or community acquired setting, and source of the bacteremia. For the present outcome study, only the first episode of bacteremia was considered. In all patients, duration of hospital and ICU stay prior to bacteremia, as well as previous antibiotic exposure, was recorded. The number and seriousness of comorbidity was assessed using the Weighted Index of Comorbidity, as developed by Charlson et al. [21]. Severity-of-illness upon ICU admission was assessed using APACHE II.

Study design

We investigated the incidence of tracheal colonization detected prior to the onset of bacteremia and its relationship with appropriate empiric therapy and outcome, defined as in-hospital mortality. The study design was approved by the ethical committee of the Ghent University Hospital. Because of the retrospective observational nature of the study, the need for informed consent was waived.

Definitions

Bacteremia was considered nosocomial when diagnosed 48 h or more after hospital admission. The sampling date of the positive blood culture was defined as onset of the bacteremia. Allocation of the source of bacteremia, i.e., pneumonia or other, was performed by the attending clinician(s) at the time of bacteremia. Pneumonia was considered as associated with bacteremia when a new or progressive pulmonary infiltrate not otherwise explained was apparent on chest X-rays, together with the presence of purulent tracheal secretions as well as respiratory deterioration defined as an increase of FiO_2 or PEEP necessary to maintain oxygenation, with exclusion of another focus of sepsis. Isolation of the same pathogen in blood cultures and respiratory cultures corroborated diagnosis, yet was not necessary for diagnosis provided that post hoc evaluation (other focus of sepsis unlikely, clinical evolution, additional radiology such as computed tomography) considered pneumonia highly probable. Pathogen prediction by tracheal surveillance was defined as the presence (detected 2 days or more before onset of bacteremia) of bacte-

ria with identical identification and antibiogram in tracheal and subsequent blood cultures.

Our ICU surveillance protocol is focused on identifying colonization of the individual patient with MDR bacteria. The following organisms were considered as MDR: methicillin-resistant *Staphylococcus aureus* (MRSA); ceftazidime-resistant Gram-negative *Enterobacteriaceae* (CAZ-R); multiple drug resistant non-fermenting organisms such as *Acinetobacter* species and *Stenotrophomonas maltophilia*, as well as *Pseudomonas aeruginosa* resistant for at least one of the following antipseudomonal antibiotics: ceftazidime; piperacillin; ciprofloxacin; and imipenem (MDR NF) [22]. In our hospital ceftazidime-resistance serves as an indicator for epidemic ESBL producing *Enterobacteriaceae* strains and/or hyper-producers of beta-lactamases [23]. Antibiotic resistance was determined according to methods recommended by the National Committee for Clinical Laboratory Standards for disk diffusion testing [24].

Surveillance of MDR pathogens is performed by routine sampling of tracheal aspirate thrice weekly in intubated patients. Further surveillance consists of culturing urine samples taken thrice weekly and anal swabs taken once weekly, but these sites were not taken into account in the present study [25]. As clinically indicated additional cultures are taken from other body sites (e.g., wounds and pressure sores). Surveillance cultures were processed according to standard procedures [26]. Screening of oral and rectal swabs is focused on resistant pathogens, while in urine samples and tracheal aspirates, a complete microbiological examination is performed. During the study period no changes in culture or surveillance methods have taken place.

Appropriate antimicrobial therapy was defined as the administration of at least one antimicrobial drug with in vitro activity against the etiological agent isolated from the blood culture. Delay > 24 h and > 48 h was defined as administration of appropriate therapy one calendar day and two or more calendar days following the date of bacteremia, respectively.

Empiric antimicrobial therapy, based on guided by primary diagnosis and co-morbidity, prior antibiotic exposure and duration of previous hospitalization, is modified according to surveillance cultures. In our ICU, the following antibiotics were prescribed empirically if surveillance cultures did not grow *Pseudomonas* or MDR organisms: a second-generation cephalosporin or amoxicillin-clavulanic acid in nosocomial pneumonia ≤ 1 week after ICU admission and without prior antibiotic exposure and an antipseudomonal betalactam in patients with prior antibiotic exposure or > 1 week ICU stay. If additional risk factors for *Pseudomonas* were present (e.g., bronchiectasis, corticosteroid therapy) or if *Pseudomonas* was isolated from SC, an antipseudomonal betalactam treatment was complemented with an aminoglycoside or a fluoroquinolone. In patients with surveillance cultures growing MDR organisms, empirical therapy, consisting essentially of an antipseudomonal betalactam or carbapenem, was broadened to cover all colonizing organisms if necessary, with addition of a glycopeptide, fluoroquinolone, aminoglycoside, trimethoprim-sulfamethoxazole, or colimycin, as appropriate.

Statistics

Continuous variables are described as mean ($\pm$ standard deviation) or median (interquartile range) depending on normal and non-normal distribution, respectively. Categorical variables are described as n (%). For comparative tests on continuous variables, the Mann–Whitney U-test and Student's t-test were used as appropriate, depending on variable distribution. For categorical variables, the Pearson chi-square test or the Fisher's exact test were used as appropriate. The major response variable used in the mortality analyses was vital status (alive or dead) at hospital discharge. Logistic regression analysis was used to assess the multivariate relationship between multiple patient characteristics and the probability of in-hospital mortality. In patients with multiple episodes of bacteremia, only the first one was considered for outcome analysis. Regression analysis was performed using enter as well as forward and backward stepwise methods. Predictors showing a $p < 0.25$ association with in-hospital mortality in univariate analysis as well as those variables that seemed clinically important were incorporated in the regression analysis. When appropriate, odds ratios (OR) and 95% confidence intervals (95% CI) are reported. To minimize the risk of collinearity affecting output, different regression models were calculated, using different sets of predictors or combining sets of predictors into a single predictor. Furthermore, a correlation matrix of the β coefficients was produced, and the Variance Inflation Factor as well as Tolerance values were calculated. The various models were tested for the presence of clinically significant interaction. Statistical analyses are executed with SPSS 11.0 (SPSS Inc., Chicago, Ill.). All tests were two-tailed and statistical significance was defined as $p < 0.05$.

Results

We identified 128 patients who developed bacteremia associated with NP; median age was 61 years (47–70 years), 64% were male. APACHE II score was 23 ($\pm$ 1). At the time of bacteremia, all patients received vasopressor therapy and 96% of them were mechanically ventilated. Prior median ICU stay was 11 days [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19].

Table 1 Bacteria isolated from blood cultures from 126 episodes of bacteremic nosocomial pneumonia and prediction in tracheal surveillance cultures 48–96 h prior (prediction). *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*

Microorganisms	Number	Prediction
Gram negative	94	65 (69)
Escherichia coli	7	5
Klebsiella sp.	17	13
Enterobacter sp.	12	10
Haemophilus influenzae	1	0
Morganella morganii	3	1
Serratia marcescens	10	8
Proteus sp.	2	1
Pseudomonas aeruginosa	28	19
Acinetobacter sp.	13	8
Stenotrophomonas maltophilia	1	0
Gram positive	32	18 (56)
MSSA	13	7
MRSA	19	11
Total	126	83 (56)

Streptococcus species other than *S. pneumoniae* and *Enterococcus* sp. are not considered; accordingly two episodes in which only these pathogens were involved are omitted

Results of blood culture isolates are summarized in Table 1. A total of 119 episodes were monomicrobial; 9 episodes were polymicrobial. Monomicrobial episodes had a Gram-positive etiology (mostly *S. aureus*) in 35 (29%), and a Gram-negative etiology in 84 (71%). In 7 cases, streptococci or enterococci were found together with a Gram-negative organism, in one case both *P. aeruginosa* and *S. maltophilia* were isolated, and one case yielded *Klebsiella pneumoniae*, *Proteus mirabilis*, and a streptococcal species. In two cases, only streptococci other than *S. pneumoniae* were involved: since surveillance obviously does not target endogenous flora, these two cases were omitted from further analysis. In 54 cases (41.5%), at least one MDR pathogen was present in blood cultures: MRSA in 19; CAZ-R in 13; and MDR NF in 22. In 95 cases (74%) tracheal aspirate taken within 24 h of the positive blood culture showed heavy growth of the same pathogen.

In 110 patients, at least one recent tracheal surveillance culture (obtained 48–96 h before bacteremia) was available: only these patients were considered for further analysis. Etiology of bacteremia was correctly predicted by a recent tracheal surveillance culture in 67 episodes (61%) and 66% of all bacteremic pathogens were isolated from these cultures (Table 1). In these 110 patients, appropriate therapy was achieved within 24 h and within 48 h in 62 and 87%, respectively. The only significant risk factor for delay of appropriate therapy > 24 h (Table 2) was a MDR etiology ($p = 0.03$), whereas prediction of etiology of bacteremia by tracheal surveillance was significantly associated with a higher rate of appropriate therapy within 24 h (71 vs 45% in patients with and

Table 2 Differences between patients ($n = 110$) with and without > 24 h delay in appropriate empirical antibiotic therapy. *MDR* multidrug resistant

Factor	No delay ($n = 68$)	> 24 h delay ($n = 42$)	p-value
Age (years)	68 (22 IQ)	42 (29 IQ)	0.24
APACHE II	23 (± 10)	25 (± 9)	0.31
MDR etiology	23 (34%)	24 (57%)	0.03
Direct Gram staining shows predominant pathogen	36 (53%)	23 (55%)	0.99
Prior detection of etiology in tracheal surveillance	49 (72%)	19 (45%)	0.01
Late (> 7 days ICU) nosocomial pneumonia	50 (74%)	29 (69%)	0.66
Hospitalization > 24 h before ICU admission	51 (75%)	29 (71%)	0.66

Table 3 Percentages of antibiotic prescriptions ≤ 48 h following bacteremia in patients ($n = 110$) with and without prediction of bacteremic etiology by tracheal surveillance cultures obtained 48–96 h prior

Antibiotic class prescribed	Prediction	No prediction	p-value
Betalactam without antipseudomonal activity	14 (21)	17 (39)	0.05
Betalactam with antipseudomonal activity	19 (29)	13 (30)	0.99
Carbapenem	17 (26)	9 (21)	0.65
Aminoglycoside [a]	12 (18)	9 (21)	0.81
Fluoroquinolone	18 (27)	13 (30)	0.83
Glycopeptide	18 (27)	8 (18)	0.36
Other [b]	11 (17)	4 (9)	0.39

Numbers in parentheses are percentages

[a] Aminoglycosides were always prescribed as part of combination therapy

[b] Other antibiotics include trimethoprim-sulfamethoxazole, colimycin and fucidin

Table 4 Characteristics in nonsurvivors and survivors of bacteremic nosocomial pneumonia (in-hospital mortality; $n = 110$). *MDR* Multidrug resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *CAZ-R* ceftazidime-resistant *Enterobacteriaceae*, *NF* nonfermenting organism

Factor	Nonsurvivors ($n = 56$)	Survivors ($n = 54$)	p-value
Age (years)	64 (54–70)	46 (39–69)	0.002
Comorbidity [a]	1 (0–2.5)	0 (0–2)	0.011
APACHE II	26 (± 10)	20 (± 8)	0.001
MDR etiology	29 (52%)	18 (34%)	0.08
MRSA	13 (23%)	5 (9%)	0.07
CAZ-R	5 (9%)	4 (7%)	0.99
MDR NF	5 (9%)	6 (11%)	0.75
Pseudomonas aeruginosa	15 (27%)	6 (11%)	0.05
Late (> 7 days ICU) nosocomial pneumonia	39 (69%)	40 (74%)	0.67
Pathogen prediction by tracheal surveillance	29 (52%)	39 (72%)	0.03
Appropriate antibiotic therapy < 24 h	31 (55%)	37 (69%)	0.17
Appropriate antibiotic therapy < 48 h	46 (82%)	50 (92%)	0.15

[a] As assessed by the Charlson Weighted Index of Comorbidity

Table 5 Results of multivariable analysis of factors affecting in-hospital mortality. *MDR* multidrug resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *CAZ-R* ceftazidime-resistant *Enterobacteriaceae*, *MDR-NF* multidrug-resistant non-fermenting organism

Predictor	OR	CI	p-value
Pathogen prediction by tracheal surveillance (unadjusted)	0.43	0.19–0.931	0.04
Model 1[a] ($n = 110$) Pathogen prediction by tracheal surveillance	0.30	0.11–0.79	0.02
Age (years)	1.05	1.01–1.08	0.01
APACHE II	1.08	1.02–1.14	0.02
MDR etiology	4.47	1.69–11.78	0.002
Constant	0.014		0.001
Model 2[b] ($n = 102$)			
Pathogen prediction by tracheal surveillance	0.32	0.12–0.82	0.02
Age (years)	1.04	1.01–1.07	0.02
APACHE II	1.08	1.02–1.15	0.01
P. aeruginosa	3.30	1.04–10.4	0.04
MRSA	5.90	1.36–25.36	0.02
Constant	0.028		0.002

Forward as well as backward stepwise procedures were performed.

[a] Parameters included were: pathogen prediction by tracheal surveillance, age, APACHE II, appropriate antibiotic therapy within 48 h, and MDR etiology of bacteremia

[b] Parameters included were as in model 1, but with inclusion of weighted index of comorbidity and replacing the parameter "MDR etiology" of model 1 by subtypes of MDR etiology (*P. aeruginosa*, MRSA, CAZ-R, MDR NF other than *P. aeruginosa*; $n = 102$)

without prediction, respectively; $p = 0.01$) but not with a higher rate of appropriate therapy at 48 h (91 vs 81% in patients with and without prediction, respectively; $p = 0.15$). Antibiotic therapy prescribed in the 48 h following bacteremia is summarized in Table 3: betalactam antibiotics without antipseudomonal activity were more frequently prescribed in patients without prediction (39 vs 21% in patients with prediction; $p = 0.05$), but the use of broad spectrum antibiotics such as carbapenems, antipseudomonal betalactams, and fluoroquinolones was similar in both groups.

Overall crude in-hospital mortality was 50%. In univariate analysis, increasing age ($p = 0.002$), severity of illness as assessed by APACHE II ($p = 0.001$), and the presence of comorbidity ($p = 0.017$) were significantly associated with increased in-hospital mortality, whereas pathogen prediction by tracheal surveillance was associated with a better outcome ($p = 0.03$; Table 4). We assessed the impact of pathogen prediction in multivariate analysis with adjusting for all clinical useful covariables which were statistically significant at the $p < 0.25$ level in univariate analysis: in two separate analyses, we adjusted for the factor MDR etiology of bacteremia and for subtypes of MDR etiology, respectively (Table 5). In both models pathogen prediction by tracheal surveillance was associated with lower mortality (OR 0.32; CI 0.12–0.83; $p = 0.02$). Odds ratios did not change after inclusion of interaction terms between predictors.

Discussion

In this retrospective observational study of bacteremia associated with NP, pathogen prediction by tracheal surveillance cultures 48–72 h prior to diagnosis was associated with the earlier institution of appropriate antimicrobial therapy. This prediction was associated with increased survival both in univariate and multivariate analysis. Moreover, the value of the odds ratio of pathogen prediction was stable in several models tested, strengthening the independency of this predictor. Overall use of broad-spectrum antibiotic classes in the first 48 h following bacteremia was similar in patients with and without prediction. It thus seems likely that earlier antibiotic coverage in colonized patients was obtained without extension of the antimicrobial spectrum or more antibiotic changes. In a previous study we have shown that in patients at risk for MDR infection, a surveillance-based early antibiotic prescription was more appropriate than a purely empirical broad-spectrum choice, without an increased consumption of broad-spectrum antibiotics [19].

It is quite generally accepted that the early institution of appropriate antimicrobial therapy determines outcome in ventilator-associated pneumonia (VAP), but the strategy by which to reach this aim is disputed [9, 10, 11, 12, 13, 15, 16, 27, 28, 29, 30, 31, 32]. Microbiological results of samples collected at suspicion of sepsis or pneumonia, whether obtained non-invasively or invasively, are of importance in modifying initial therapy in order to limit the continued use of unnecessary broad spectrum antibiotics, but these modifications have limited impact on direct outcome [9, 11]. On the other hand, our study shows that pathogen prediction by surveillance cultures decreases time lag of appropriate antimicrobial coverage, as more patients were adequately treated within the first 24 h following bacteremia. As surveillance was directed at the early tracing of MDR colonization, this advantage was especially true for episodes caused by MDR strains, with doubling of early (< 24 h) adequate antimicrobial coverage when predicted (64 vs 32%; $p = 0.04$). Within 48 h this difference had disappeared, with adequate coverage of 86 and 84% of MDR episodes, respectively, likely due to the availability of diagnostic culture results. Yet, in hospital mortality was lower in patients with pathogen prediction through surveillance cultures (42 vs 61%; $p = 0.04$). This suggests that the critical time window for the institution of adequate antibiotic therapy in our bacteremic patients was < 24 h rather than < 48 h. Similarly, Iregui et al. observed a detrimental effect of delaying appropriate antibiotic therapy for > 24 h on in-hospital mortality using a multivariable analysis. All patients eventually received adequate therapy, although the time frame in which this was reached was not specified [12].

As observed in our study and other [9, 11, 33, 34, 35], drug resistance is a risk factor for delayed appropriate antimicrobial therapy. In a multicenter study on VAP in postoperative patients, Gram-negative non-fermenting pathogens were associated with delayed therapy [34]. Kollef observed that initial antimicrobial treatment was inappropriate in 60% of patients with MRSA infection vs 9% of patients with methicillin-sensitive *S. aureus* (MSSA) infection [35]. Consequently, the revised guidelines for the management of hospital-acquired pneumonia advocate the use of a broad spectrum empirical spectrum (consisting of the combination of a broad spectrum beta-lactam or carbapenem, together with an antipseudomonal fluoroquinolone or aminoglycoside and a glycopeptide or linezolid) if risk factors for MDR are present [36]. As the overall majority (109 of 110) of our patients possessed at least one risk factor for MDR, this strategy would have lead to a far greater antibiotic "burden" within the first 48 h following bacteremia. Previously, we have shown that this strategy, as compared with the current, surveillance-guided, antibiotic prescription, had inferior adequacy in the subset of patients at the highest risk for MDR (i.e., both prior antibiotic therapy and a prolonged (> 1 week) ICU stay [19].

In our population, microbial aetiology of bacteremia affected outcome, as both MRSA and, to a lesser extent, *P. aeruginosa* were identified as independent predictors of mortality, even after adjustment for early appropriate antimicrobial therapy. Conflicting data exist in the literature whether methicillin resistance represents an independent risk factor for a poor outcome in *S. aureus* infection. In a previous matched-cohort study, we found a significant 22% increase in attributable mortality of MRSA compared with MSSA bacteremia [37]; however, the most recent multivariable analysis in staphylococcal VAP could not identify methicillin resistance as an independent predictor of mortality [38]. In our population, administration of glycopeptides was delayed for > 48 h in 32% of cases, which could have contributed to a high in-hospital mortality of 68.4%; however, no difference was observed in mortality in MRSA episodes treated early with glycopeptides vs episodes with delayed therapy. Possible explanations for this lack of difference in mortality include a small sample size as well as a lack of clinical efficacy of glycopeptides in pneumonia, an observation which has already been linked with poor penetration of glycopeptides in the lung [39, 40].

In our present study, in-hospital mortality in *P. aeruginosa* bacteremia associated with NP was 66.7%, which is similar to the 71.4% mortality in pneumonia caused by *Pseudomonas* or *Acinetobacter* species reported by Fagon et al. [7]. In our, episodes of *P. aeruginosa* bacteremia were treated with combination therapy of two antipseudomonal antibiotics within 48 h in 67% (16 of 24). Crude in-hospital mortality was not significantly different in patients treated with combination therapy vs single or delayed antibiotic therapy (69 vs 63%, respectively; $p =$ NS).

Our study had several limitations. Firstly, our strategy of surveillance, with culturing of endotracheal aspirate immediately following intubation followed by a thrice weekly sampling, resulted in a rather moderate 66% anticipation of microbial etiology, although this figure is still markedly higher than that reported in two recent trials, with 33% reported by Hayon et al. [41], and a very low figure (one of every 28 episodes predicted) by Bouza et al. [42]. As we only considered tracheal surveillance cultures from 48–72 h prior to bacteremia, a higher sampling frequency and hence shorter time interval between data may have contributed to a higher positive predictive value [43].

Interestingly, a recent study using tracheal surveillance twice weekly reported a very high (83%) prediction of VAP etiology, as identified by quantitative culture of broncho-alveolar lavage fluid [44]. Our lower prediction is probably largely explained by the fact that we compared blood cultures, rather than BAL, with prior tracheal surveillance cultures. Moreover, 82% of our patients had received antibiotic treatment in the week prior to bacteremia which again is known to interfere with microbiological cultures.

Secondly, although pathogen prediction improved early antibiotic prescription in our analysis, and probably improved outcome through this mechanism, early appropriate therapy itself was not associated with improved survival in univariate nor multivariate analysis. As our analysis was done on a limited sample size of 110 patients, underpowering may be responsible for this. Alternatively, as discussed above, this apparent contradiction could be due to the low resolution of the time frame of appropriate therapy in our study. In severe infection, appropriate antimicrobials should probably be administered within hours, rather than days, to optimize odds for survival, as has been observed in outpatients with severe community-acquired pneumonia [45], and recently, in patients with septic shock [46].

Finally, diagnostic misclassification in our retrospective study may be of concern; however, all cases included were identified prospectively, and the source of bacteremia was determined at the time of bacteremia integrating clinical, radiological, and microbiological data, with post-hoc removal of the case if a different source of bacteremia was ultimately defined. According to a recent consensus conference, all our cases could be classified as microbiologically confirmed pneumonia [47]; however, we think it may be more conservative to refer to our cases as bacteremia associated with pneumonia, rather than bacteremic pneumonia. Hence, our results potentially only apply to a small subset of NP, at increased risk though for a poor outcome [35, 48]. It should be noted that we relied on semiquantitative, rather than quantitative, culture results of endotracheal aspirate in our diagnostic work-up. Since the primary aim of quantitative culturing is to distinguish colonization from infection, this limitation probably does not affect the degree of certainty of the microbiological diagnosis, since all patients had positive blood cultures by inclusion.

Our results suggest that pathogen prediction by tracheal surveillance cultures increases the rate of early adequate empiric antibiotic therapy in bacteremia associated with nosocomial pneumonia. This prediction may also influence impact outcome.

Acknowledgements. The authors thank G. Verschraegen and J. De Schuymer (Department of Nursing) for their important contribution in registering the episodes of bacteremia during the study period, as well as G. Van Maele (Department of Medical Informatics and Statistics, Ghent University) for his help in the statistical analysis. This study was supported by a clinical doctoral grant Fund for Scientific Research Flanders (1.7.201.07.N.00 to P.D.).

References

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolaschanoin MH, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) Study. J Am Med Assoc 274:639–644
2. National Nosocomial Infections (NNIS) system (2001) Data summary from Jan 1992-June 2001. Am J Infect Control 29:408–421
3. Vincent JL (2003) Nosocomial infections in adult intensive-care units. Lancet 361:2068–2077
4. Hernandez G, Rico P, Diaz E, Rello J (2004) Nosocomial lung infections in adult intensive care units. Microbes and Infection 6:1004–1014
5. Rello J, Rue M, Jubert P, Muses G, Sonora R, Valles J, Niederman MS (1997) Survival in patients with nosocomial pneumonia: impact of the severity of illness and the etiologic agent. Crit Care Med 25:1862–1867
6. Rello J, Jubert P, Valles J, Artigas A, Rue M, Niederman MS (1996) Evaluation of outcome for intubated patients with pneumonia due to *Pseudomonas aeruginosa*. Clin Infect Dis 23:973–978
7. Fagon J, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C (1993) Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 94:281–288
8. Rello J, Torres A, Ricart M, Valles J, Gonzalez J, Artigas A, Rodriguezroisin R (1994) Ventilator-associated pneumonia by *Staphylococcus aureus*: comparison of methicillin-resistant with methicilline sensitive episodes. Am J Respir Crit Care Med 150:1545–1549

9. Luna CM, Vujacich P, Niederman M, Vay C, Gherardi C, Matera J, Jolly EC (1997) Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 111:676–685
10. Rello J, Gallego M, Mariscal D, Sonora R, Valles J (1997) The value of routine microbiological investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 156:196–200
11. Kollef M, Ward S (1998) The influence of mini-BAL cultures on patient outcome: Implications for the antibiotic management of ventilator-associated pneumonia. Chest 113:412–420
12. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH (2002) Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122:262–268
13. Wunderink R (1993) Mortality and ventilator-associated pneumonia. The best antibiotics may be the least antibiotics. Chest 104:993–995
14. Fridkin S, Gaynes R (1999) Antimicrobial resistance in intensive care units. Clin Chest Med 20:303–316
15. Höffken G, Niederman M (2002) Nosocomial pneumonia: the importance of a de-escalation strategy for antibiotic treatment of pneumonia in the ICU. Chest 122:2183–2196
16. Paterson D, Rice L (2003) Empirical antibiotic choice for the seriously ill patient: Are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? Clin Infect Dis 36:1006–1012
17. Rello J, Vidaur L, Sandiumenge A, Rodriguez A, Gualis B, Boque C, Diaz E (2004) De-escalation therapy in ventilator-associated pneumonia. Crit Care Med 32:2183–2190
18. Blot S, Depuydt P, Vogelaers D, Decruyenaere J, De Waele J, Hoste E, Peleman R, Claeys G, Verschraegen G, Colardyn F, Vandewoude K (2005) Colonization status and appropriate antibiotic therapy in nosocomial bacteremia caused by antibiotic-resistant Gram-negative bacteria in the ICU. Infect Control Hosp Epidemiol 26:575–579
19. Depuydt P, Blot S, Benoit D, Claeys G, Verschraegen G, Vandewoude K, Vogelaers D, Decruyenaere J, Colardyn F (2006) Antimicrobial resistance in nosocomial blood stream infection associated with pneumonia and the value of systematic surveillance cultures in an adult intensive care unit. Crit Care Med 34:653–659
20. Depuydt P, Blot S, Benoit D, Vogelaers D, Claeys G, Verschraegen G, Vandewoude K, Decruyenaere J, Blot S (2005) Outcome in bacteremic nosocomial pneumonia and the value of regular tracheal surveillance cultures. Program and abstracts of the 45th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), Washington, A299
21. Charlson M, Pompei P, Ales K, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
22. Carmeli Y, Troillet N, Eliopoulos GM, Samore MH (1999) Emergence of antibiotic-resistant *Pseudomonas aeruginosa*. Comparison of risks associated with different antipseudomonal agents. Antimicrob Agents Chemother 43:1379–1382
23. Blot S, Vandewoude K, De Bacquer D, Colardyn F (2002) Nosocomial bacteremia caused by antibiotic-resistant Gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization. Clin Infect Dis 34:1600–1606
24. NCCLS (2003) Performance standards for antimicrobial disk susceptibility tests. Approved standard M2-A8. Wayne
25. Blot S, Vandewoude K, Colardyn F (2000) Prevalence and risk factors for colonisation with Gram-negative bacteria in an intensive care unit. Acta Clin Belg 55:249–256
26. Murray P, Barron E, Jorgensen J, Pfaller M, Yolken R (eds) (2003) Manual of clinical microbiology, 8th edn. ASM Press, Washington, DC
27. Rello J, Diaz E (2003) Pneumonia in the intensive care unit. Crit Care Med 31:2544–2551
28. Alvarez-Lerma F for the ICU-Acquired Pneumonia Study Group (1996) Modifications of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. Intensive Care Med 22:387–394
29. Blot S, Vandewoude K (2004) Early detection of systemic infections. Acta Clin Belg 59:20–23
30. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: a randomized trial. Ann Intern Med 132:621–630
31. Brun-Buisson C, Fartoukh M, Lechapt E, Honore S, Zahar JR, Cerf C, Maitre B (2005) Contribution of blinded, protected quantitative specimens to the diagnostic and therapeutic management of ventilator-associated pneumonia. Chest 128:533–544
32. Colardyn F (2005) Appropriate and timely empirical antimicrobial treatment of ICU infections: a role for carbapenems. Acta Clin Belg 60:51–62
33. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118:146–155
34. Dupont H, Montravers P, Gauzit M, Veber B, Pouriat JL, Martin C (2003) Outcome of postoperative pneumonia in the Eole study. Intensive Care Med 29:179–188
35. Kollef M, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462–474
36. American Thoracic Society (2005) Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health-care associated pneumonia. Am J Respir Crit Care Med 171:388–416
37. Blot S, Vandewoude K, Hoste E, Colardyn F (2002) Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. Arch Intern Med 162:2229–2235
38. Combes A, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Gibert C, Chastre J (2004) Impact of methicillin resistance on outcome of *Staphylococcus aureus* ventilator-associated pneumonia. Am J Respir Crit Care Med 170:786–792
39. Wunderink R, Rello J, Cammarata S, Croos-Dabrera R, Kollef MH (2003) Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 124:1789–1797
40. Niederman M (2001) Impact of antibiotic resistance on clinical outcomes and the cost of care. Crit Care Med(Suppl):S114–S120
41. Hayon J, Figliolini C, Combes A, Trouillet JL, Kassis N, Dombret MC, Gibert C, Chastre J (2002) Role of serial routine microbiologic culture results in the initial management of ventilator-associated pneumonia. Am J Respir Crit Care Med 165:41–46

42. Bouza E, Perez A, Munoz P, Perez J, Rincon C, Sanchez C, Martin-Rabadan P, Riesgo M (2003) Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. Crit Care Med 31:1964–1970
43. Crnich C, Proctor R (2003) Ventilator-associated pneumonia: Does surveillance have a role in its management. Crit Care Med 31:2411–2412
44. Michel F, Franceschini B, Berger P, Arnal JM, Gainnier M, Sainty JM, Papazian L (2005) Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. Chest 127:589–597
45. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG (2004) Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 164:637–644
46. Kumar A, Roberts D, Wood K, Light B, Parillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in septic shock. Crit Care Med 34:1589–1596
47. Calandra T, Cohen J (2005) The International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit. Crit Care Med 33:1538–1548
48. Bryan CS, Reynolds KL (1984) Bacteremic nosocomial pneumonia. Analysis of 172 episodes from a single metropolitan area. Am Rev Respir Dis 129:668–671