Clinical Infectious Diseases

MAJOR ARTICLE

Ceftazidime, Carbapenems, or Piperacillin-tazobactam as Single Definitive Therapy for *Pseudomonas aeruginosa* Bloodstream Infection: A Multisite Retrospective Study

Tanya Babich,[1] Pontus Naucler,[2] John Karlsson Valik,[2] Christian G. Giske,[3] Natividad Benito,[4] Ruben Cardona,[5] Alba Rivera,[6] Celine Pulcini,[7,8] Manal Abdel Fattah,[8] Justine Haquin,[8] Alasdair Macgowan,[9] Sally Grier,[9] Julie Gibbs,[9] Bibiana Chazan,[10] Anna Yanovskay,[10] Ronen Ben Ami,[1,11] Michal Landes,[11] Lior Nesher,[12] Adi Zaidman-Shimshovitz,[12] Kate Mccarthy,[13] David L. Paterson,[13] Evelina Tacconelli,[14] Michael Buhl,[14] Susanna Mauer,[14] Jesus Rodriguez-Bano,[15] Isabel Morales,[15] Antonio Oliver,[16] Enrique Ruiz De Gopegui,[16] Angela Cano,[17] Isabel Machuca,[17] Monica Gozalo-Marguello,[18] Luis Martinez Martinez,[18] Eva M. Gonzalez-Barbera,[19] Iris Gomez Alfaro,[19] Miguel Salavert,[20] Bojana Beovic,[21] Andreja Saje,[21] Manica Mueller-Premru,[22] Leonardo Pagani,[23] Virginie Vitrat,[24] Diamantis Kofteridis,[25] Maria Zacharioudaki,[25] Sofia Maraki,[25] Yulia Weissman,[1] Mical Paul,[26] Yaakov Dickstein,[26] Leonard Leibovici,[27] and Dafna Yahav[28]

[1]Sackler Faculty of Medicine, Tel Aviv University, Israel; [2]Division of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet, and Department of Infectious Diseases, Karolinska University Hospital, and [3]Department of Laboratory Medicine, Karolinska Institutet, and Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden; [4]Infectious Diseases Unit, Department of Internal Medicine, Hospital de la Santa Creu i Sant Pau—Institut d'Investigació Biomèdica Sant Pau, Universitat Autònoma de Barcelona, [5]Department of Internal Medicine, Hospital de la Santa Creu i Sant Pau, [6]Department of Microbiology, Hospital de la Santa Creu i Sant Pau—Institut d'Investigació Biomèdica Sant Pau, Barcelona, Spain; [7]APEMAC and [8]CHRU-Nancy, Infectious Diseases Department, Université de Lorraine, France; [9]Department of Infection Sciences, Southmead Hospital, Bristol, United Kingdom; [10]Infectious Diseases Unit, Emek Medical Center, Afula, Rappaport Faculty of Medicine, Technion, Haifa, [11]Infectious Diseases Unit Sourasky Medical Center, Tel-Aviv, and [12]Infectious Disease Institute, Soroka Medical Center, Ben-Gurion University of the Negev, Beer Sheba, Israel; [13]UQ Centre for Clinical Research, The University of Queensland, Brisbane, Australia; [14]Division of Infectious Diseases, Tübingen University Hospital, Germany; [15]Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla, [16]Servicio de Microbiología and Unidad de Investigación, Hospital Universitario Son Espases, Instituto de Investigación Illes Balears (IdISBa), Palma de Mallorca, [17]Infectious Diseases Unit, Maimonides Biomedical Research Institute of Cordoba, Reina Sofia University Hospital, University of Cordoba, [18]Microbiology Service, University Hospital Marqués de Valdecilla–IDIVAL, Santander, [19]Microbiology Department, La Fe University Hospital, Valencia, and [20]Infectious Diseases Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain; [21]Department of Infectious Diseases, University Medical Centre, Faculty of Medicine, University of Ljubljana, and [22]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia; [23]Infectious Diseases Unit, Bolzano Central Hospital, Italy; [24]Infectious Diseases Unit, Annecy-Genevois Hospital Center, Annecy, France; [25]Infectious Disease Unit, Department of Internal Medicine, University Hospital of Heraklion, Crete, Greece; [26]Infectious Diseases Unit, Rambam Health Care Campus, Haifa, and [27]Medicine E and [28]Infectious Diseases Unit, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel

Background. The optimal antibiotic regimen for *Pseudomonas aeruginosa* bacteremia is controversial. Although β-lactam monotherapy is common, data to guide the choice between antibiotics are scarce. We aimed to compare ceftazidime, carbapenems, and piperacillin-tazobactam as definitive monotherapy.

Methods. A multinational retrospective study (9 countries, 25 centers) including 767 hospitalized patients with *P. aeruginosa* bacteremia treated with β-lactam monotherapy during 2009–2015. The primary outcome was 30-day all-cause mortality. Univariate and multivariate, including propensity-adjusted, analyses were conducted introducing monotherapy type as an independent variable.

Results. Thirty-day mortality was 37/213 (17.4%), 42/210 (20%), and 55/344 (16%) in the ceftazidime, carbapenem, and piperacillin-tazobactam groups, respectively. Type of monotherapy was not significantly associated with mortality in either univariate, multivariate, or propensity-adjusted analyses (odds ratio [OR], 1.14; 95% confidence interval [CI], 0.52–2.46, for ceftazidime; OR, 1.3; 95% CI, 0.67–2.51, for piperacillin-tazobactam, with carbapenems as reference in propensity adjusted multivariate analysis; 542 patients). No significant difference between antibiotics was demonstrated for clinical failure, microbiological failure, or adverse events. Isolation of *P. aeruginosa* with new resistance to antipseudomonal drugs was significantly more frequent with carbapenems (36/206 [17.5%]) versus ceftazidime (25/201 [12.4%]) and piperacillin-tazobactam (28/332 [8.4%] ($P = .007$).

Conclusions. No significant difference in mortality, clinical, and microbiological outcomes or adverse events was demonstrated between ceftazidime, carbapenems, and piperacillin-tazobactam as definitive treatment of *P. aeruginosa* bacteremia. Higher rates of resistant *P. aeruginosa* after patients were treated with carbapenems, along with the general preference for carbapenem-sparing regimens, suggests using ceftazidime or piperacillin-tazobactam for treating susceptible infection.

Keywords. *Pseudomonas*; bacteremia; beta-lactam; monotherapy.

Received 16 January 2019; editorial decision 9 May 2019; accepted 16 July 2019; published online July 17, 2019.

Presented in part: This study was presented as poster presentation at the European Society of Clinical Microbiology and Infectious Diseases annual conference, Madrid, Spain, 21–24 April 2018.

Correspondence: D. Yahav, Infectious Diseases Unit, Rabin Medical Center, Beilinson Hospital, 39 Jabotinsky Road, Petah-Tikva, 49100 Israel (dafna.yahav@gmail.com).

Clinical Infectious Diseases® 2020;70(11):2270–80

DOI: 10.1093/cid/ciz668

Pseudomonas aeruginosa infections are common, especially in hospitalized and immunocompromised hosts, with 2–4% of hospital-acquired bloodstream infections caused by this pathogen [1, 2]. *Pseudomonas aeruginosa* bacteremia is associated with high mortality rates, ranging from 20% to 40% for 30-day mortality in different studies [3, 4].

Several studies have demonstrated inappropriate empiric antibiotic treatment as a risk factor for mortality in *P. aeruginosa* bacteremia [4–7]. However, the optimal empirical and

definitive antibiotic regimens for this infection are yet to be defined. One of the most controversial management questions of *P. aeruginosa* bacteremia involves the use of combination versus monotherapy regimens as empiric and definitive treatment. Current data demonstrate no mortality benefit using 2 active antipseudomonal agents over a single active agent as definitive therapy [8–10].

Another unresolved question is whether any specific antipseudomonal β-lactam is preferable as monotherapy for *P. aeruginosa* bacteremia. Data directly comparing different active antibiotics are scarce and consist of few small retrospective studies demonstrating no significant difference in mortality or clinical success among different monotherapies [11–13]. Regarding indirect comparative data, among patients with *P. aeruginosa* pneumonia, a systematic review demonstrated lower clinical and microbiological cure rates among patients treated with imipenem compared with other monotherapies, relating this observation to a higher resistance development rate with imipenem [14]. Other direct comparisons are not available and American and European guidelines for the treatment of hospital-acquired and ventilator-associated pneumonia do not recommend a specific antibiotic class to target *P. aeruginosa* due to the lack of evidence [15, 16].

Considering the drugs commonly used as monotherapy for *P. aeruginosa* bacteremia [17, 18], the use of carbapenems has been associated with the development of carbapenem-resistant bacteria [19, 20] and higher rates of *Clostridioides difficile*–associated diarrhea compared with β-lactam β-lactamase inhibitors [21]. Cephalosporins have been reported as a risk factor for extended-spectrum β-lactamase–producing bacteria [22], methicillin-resistant *Staphylococcus aureus* (MRSA) infections [23], carbapenem-resistant bacteria [20], and *Clostridium difficile* infection [24].

Hence, clinical studies comparing different monotherapies are few [11–13]. The β-lactams usually used for this infection vary in their potential to cause collateral damage and adverse events. We aimed to compare the efficacy and safety of ceftazidime, carbapenems, and piperacillin-tazobactam for the definitive treatment of *P. aeruginosa* bacteremia.

METHODS

Data Collection

This was a retrospective, observational, multinational, and multicenter cohort study. Data were collected from 25 centers in 9 countries across Europe, Australia and Israel (see Supplementary Table 1 for details on participating centers). Data collection was approved by the medical ethical committee of each participating center. The study involved the collection of data of hospitalized patients from 1 January 2009 until 31 October 2015. Data collected included baseline characteristics of patients (demographics, comorbidities according to the Charlson comorbidity index, functional capacity, immunosuppression), infection characteristics (duration of hospitalization prior to bacteremia onset, department of hospitalization at time of culture collection, date of onset, source, place of acquisition, sequential organ failure assessment [SOFA] score at onset), treatment data (type of empirical and definitive therapy, dose, duration), microbiological data (susceptibility profile), and outcomes (see below).

Patient Inclusion

Patient aged 18 years or older with monomicrobial *P. aeruginosa* bacteremia during hospitalization were considered for inclusion. Patients were identified using blood culture data from the microbiology laboratory information systems of each center. *Pseudomonas aeruginosa* bacteremia was defined by growth of *P. aeruginosa* in 1 or more blood culture bottles. We included in the analysis patients who were treated with ceftazidime, carbapenem, or piperacillin-tazobactam as definitive monotherapy (see below). Any empirical therapy was allowed (monotherapy or combination with any antibiotics), provided that criteria for definitive monotherapy were fulfilled for the initial/subsequent antibiotics.

Data were retrieved from medical records of all consecutive patients identified with *P. aeruginosa* bacteremia. Patients with polymicrobial infections or recurrent episodes were excluded (each patient was included once).

Definitions

Definitive monotherapy: Antibiotic therapy was considered definitive monotherapy if an antipseudomonal drug with in vitro activity against the isolated strain was administered as the only drug to the patient for at least 72 hours in the first week following culture collection, with no other antipseudomonal drug administered for more than 72 hours during the first week. Concomitant antipseudomonal drug for more than 48 hours was considered combination therapy and such cases were excluded. A list of antipseudomonal drugs is given in Appendix 1. Patients who were stepped down to fluoroquinolones following at least 72 hours of a β-lactam were still considered as receiving β-lactam monotherapy.

Appropriate treatment: Appropriate treatment was defined as an antipseudomonal antibiotic to which the pathogen was susceptible in vitro (as determined by the local laboratory; see Supplementary Table 1). Appropriate empirical therapy was defined as appropriate treatment as above that was administered within 48 hours of culture collection.

Maximal drug dosage: For each β-lactam included we defined maximal vs nonmaximal dosage according to definitions detailed in Appendix 2.

Immunosuppressive therapy: This included chemotherapy or other immunosuppressant therapy in the 30 days prior to infection onset, chronic therapy with corticosteroids (10

mg prednisone or equivalent daily for more than 30 consecutive days), organ transplantation, or hematopoietic stem cell transplantation.

Isolation of a P. aeruginosa strain with new resistance: Isolation of *P. aeruginosa* (colonization or infection) of any site with new resistance that was not apparent in the original isolate to any of the following within 30 days—aminoglycosides, carbapenems, ceftazidime, antipseudomonal penicillins, or fluoroquinolones.

Outcomes

The primary outcome was 30-day all-cause mortality following the first positive blood culture. Secondary outcomes included 7-day all-cause mortality, 7-day clinical failure (defined as any of the following: abnormal low blood pressure [systolic <90 mmHg or mean arterial pressure <70 mmHg], abnormal low arterial oxygen saturation [<90% room air], temperature >38°C, or death), microbiological failure, late septic shock, late need for respiratory support, fever duration, hospitalization duration, isolation of a *P. aeruginosa* strain with new resistance, emergent resistance among other gram-negative and gram-positive pathogens, and adverse events. For detailed definitions of each of the secondary outcomes, see Appendix 3.

Statistical Analysis

The chi-square or Fisher's exact tests were used to compare categorical data and the Student's *t* test/1-way analysis of variance, or Mann-Whitney *U* test/Kruskal-Wallis for continuous data, as appropriate (the Kolmogorov-Smirnoff test was used to test whether the distribution of a continuous variable was normal). Logistic regression analysis was performed to identify independent variables associated with mortality. Variables with $P < .05$ in univariate analysis were included in the multivariate model to control for confounding. Missing variables were completed using multiple imputations [25]. Statistically significant covariates were tested for collinearity. For the multivariate analysis, the generalized estimating equation binary logistics was used in order to control for a possible effect of the reporting medical center, entered as a random-effect variable.

A multiple propensity score analysis was conducted, using a multinomial logistic regression, in order to adjust for possible confounders affecting the choice of the treatment drug. All statistically significant variables ($P < .1$) in Table 1 were used for the propensity score analysis. The propensity for receiving each antipseudomonal drug was calculated for each patient. We then trimmed 10% from the edge of the propensity scores for a better balance between groups. The propensity scores were introduced into the multivariate analysis of predictors of 30-day mortality [26]. Six different models were tested, using the quasi-likelihood under the independence model criterion (QIC) in order to fit the best model.

All tests were 2-tailed, and a *P* value less than .05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS statistics 24 software.

RESULTS

The entire database consisted of 2396 consecutive patients with documented *P. aeruginosa* bacteremia. Among these patients, 767 were treated with definitive monotherapy according to the study's definition and entered into the analysis (see Figure 1 for the study flowchart). Of these, 213 patients were treated with ceftazidime as the definitive monotherapy, 210 with carbapenems (166 meropenem, 44 imipenem), and 344 with piperacillin-tazobactam.

Baseline characteristics of included patients by type of monotherapy and infection characteristics are presented in Table 1. Among the entire cohort, the median age was 68 years (interquartile range, 58–78) and 245 patients (31.9%) were women. Patients treated with ceftazidime were less likely to receive chemotherapy or be neutropenic, had higher albumin levels, a lower comorbidity index, and a lower SOFA score compared with patients treated with other β-lactams. Patients treated with carbapenems were younger, more likely to be women, more likely to be hospitalized in the intensive care unit (ICU), carry a nasogastric tube or endotracheal tube/tracheostomy at presentation of infection, and have previous surgery within 30 days prior to presentation.

Primary Outcome: 30-Day All-cause Mortality

Among 767 patients included, 134 patients (17.5%) died within 30 days. The type of definitive monotherapy was not a significant risk factor for mortality in univariate analysis. All-cause 30-day mortality per study group was 37 of 213 (17.4%) in the ceftazidime group, 42 of 210 (20%) in the carbapenem group, and 55 of 344 (16%) in the piperacillin-tazobactam group ($P = .483$) (Table 2). Significant risk factors for mortality in univariate analysis included bedridden functional capacity, nasogastric tube or endotracheal tube/tracheostomy at baseline, hospitalization in the previous 90 days, current hospitalization in the ICU, high Charlson comorbidity index, solid metastatic tumor, nosocomial infection, high SOFA score, low serum albumin, high heart rate, and low systolic blood pressure at infection presentation. A urinary tract source of bacteremia was protective while a pulmonary source predicted mortality. Using a maximal dose of β-lactams (see Appendix 2 for definition) did not decrease mortality. A separate analysis of the interaction between maximal dose and severity of infection, as represented by SOFA score, did not demonstrate decreased mortality using maximal antibiotic doses among patients with higher SOFA scores. Appropriate empirical therapy was not associated with increased mortality (80 of 571 [14%] surviving patients received

Table 1. Baseline Patient and Infection Characteristics by Type of Antibiotic Monotherapy

Variable	Ceftazidime (n = 213)	Piperacillin-Tazobactam (n = 344)	Carbapenem (n = 210)	Total Cohort (n = 767)	*P*
Demographic characteristics					
Age, y	68 (57–80)	69 (59–78)	66 (56–76)	68 (58–78)	.042
Weight (N = 457), kg	70 (59–82)	73 (62–84)	71 (62.5–82.5)	72 (62–83.25)	.267
Height (N = 415), m	1.69 ± 0.1	1.70 ± 0.09	1.68 ± 0.08	1.69 ± 0.09	.396
Female gender, n (%)	59 (27.7)	106 (30.8)	80 (38.1)	245 (31.9)	.06
Department at time of culture collection—ICU, n/N (%)	33 (15.5)	38/343 (11.1)	56 (26.7)	127/766 (16.6)	<.01
Bedridden at baseline, n/N (%)	6/193 (3.1)	17/328 (5.2)	13/186 (7)	36/707 (5.1)	.227
Arrival from nursing home/long-term care facility, n/N (%)	18/212 (8.5)	25 (7.3)	23/209 (11)	66/765 (8.6)	.315
Previous hospitalization (90 days), n/N (%)	121/210 (57.6)	191/339 (56.3)	116/207 (56)	428/756 (56.6)	.137
Devices at infection onset					
Endotracheal/tracheostomy tube, n (%)	31 (14.6)	24 (7)	38 (18.1)	93 (12.1)	.000
Arterial line, n (%)	25 (11.7)	31 (9)	39 (18.7)	95 (12.4)	.004
Central venous line, n/N (%)	85 (39.9)	133/342 (38.9)	96/209 (45.9)	314/764 (41.1)	.243
Nasogastric tube, n (%)	38 (19.7)	44 (13.4)	42 (22.5)	124 (17.5)	.021
Urinary catheter, n (%)	87 (40.8)	127 (37.1)	92 (43.8)	306 (40)	.286
Any other foreign device,[a] n (%)	34 (16)	80 (23.4)	48 (22.9)	162 (21.2)	.089
Baseline characteristics					
Chemotherapy previous 30 days, n (%)	33 (15.5)	112 (32.6)	61 (29.2)	206 (26.9)	.000
Steroid therapy,[b] n/N (%)	30/212 (14.2)	62/342 (18.1)	48 (22.9)	140 (18.3)	.069
Previous surgery (30 days), n (%)	56 (26.3)	83 (24.1)	72 (34.3)	211 (27.5)	.031
Chronic dialysis, n (%)	12 (5.7)	14 (4.1)	12 (5.7)	38 (5)	.582
Intravenous drug use, n (%)	11 (5.2)	3 (0.9)	4 (1.9)	18 (2.4)	.004
Neutropenia, n (%)	25 (11.7)	75 (21.8)	47 (22.4)	147 (19.2)	.005
Charlson score (N = 743)	2 (1–6)	4.5 (2–6)	3 (1–6)	3 (1–6)	.003
Hospital-acquired infection, n (%)	109 (51.2)	163 (47.4)	121 (57.6)	393 (51.2)	.065
Sepsis presentation					
Source of bacteremia, n (%)	(N = 210)	(N = 342)	(N = 210)	(N = 762)	.137
Unknown	49 (23.3)	63 (18.4)	42 (20)	154 (20.2)	
Abdominal	12 (5.7)	40 (11.7)	10 (4.8)	62 (8.1)	
Line-associated	46 (21.9)	77 (22.5)	43 (20.5)	166 (21.8)	
Pulmonary	27 (12.9)	48 (14)	37 (17.6)	112 (14.7)	
Skin, soft tissue, bone, and joints	18 (8.6)	26 (7.6)	21 (10)	65 (8.5)	
Urinary	52 (24.8)	78 (22.8)	55 (26.2)	185 (24.3)	
Other	6 (2.9)	10 (2.9)	2 (1)	18 (2.4)	
SOFA score (N = 687)	3 (2–5)	4 (2–6)	4 (2–6)	4 (2–6)	.038
MDR *Pseudomonas*, n (%)	18 (8.5)	14 (4.1)	26 (12.4)	58 (7.6)	.001
Temperature (N = 736), °C	38.5 ± 0.96	38.5 ± 1.04	38.5 ± 1.005	38.49 ± 1.01	.963
Heart rate (N = 661), beats per minute	103.33 ± 22.01	106.63 ± 22.49	107.51 ± 22.89	105.99 ± 22.5	.172
Systolic blood pressure (N = 726), mmHg	104.16 ± 22.9	101.4 ± 22.9	102.08 ± 23.86	102.3 ± 23.6	.427
Diastolic blood pressure (N = 667), mmHg	56.5 (47–65)	56 (50–62)	57.5 (48.25–65)	56 (49–64)	.932
Leukocytes (N = 742), $\times 10^9$/L	11.09 (6.4–16.77)	10.5 (2.07–18.2)	10.6 (2.2–17.8)	10.68 (3.12–17.7)	.375
Serum creatinine (N = 739), mg/dL	1.14 (0.76–1.8)	1.17 (0.8–1.82)	1.1 (0.76–1.99)	1.14 (0.78–1.9)	.907
Serum albumin (N = 476), g/dL	2.8 (2.3–3.4)	2.6 (2.2–3. 2)	2.6 (2–3.1)	2.7 (2.2–3.1)	.006
Management					
Intermittent administration (vs continuous/extended), n/N (%)	176/211 (83.4)	281/341 (81.4)	176/208 (84.6)	633/760 (83.3)	.796
Inappropriate empirical treatment (<48 hours), n/N (%)	35/189 (18.5)	40/315 (12.7)	20/193 (10.4)	95/697 (13.6)	.054
Maximal dosage,[c] n/N (%)	111/201 (55.2)	86/315 (27.3)	86/202 (42.6)	283/718 (39.4)	<.001
Total duration of monotherapy, days	7 (4.5–11)	7 (4–10.75)	8 (5–11)	7 (4–11)	.046

Continuous variables are presented as median (IQR) or mean ± SD according to distribution of variable; categorical variables are presented as no. (%).
Abbreviations: ICU, intensive care unit; IQR, interquartile range; MDR, multidrug resistance; SD, standard deviation; SOFA, sequential organ failure assessment.

[a]Any other foreign device, including prosthetic joint, prosthetic valve, implantable cardiovascular device, or vascular graft.

[b]Steroid therapy: defined as 10 mg prednisone or equivalent daily for more than 30 consecutive days.

[c]Definitions of maximal doses of definitive antibiotics are presented in Appendix 2.

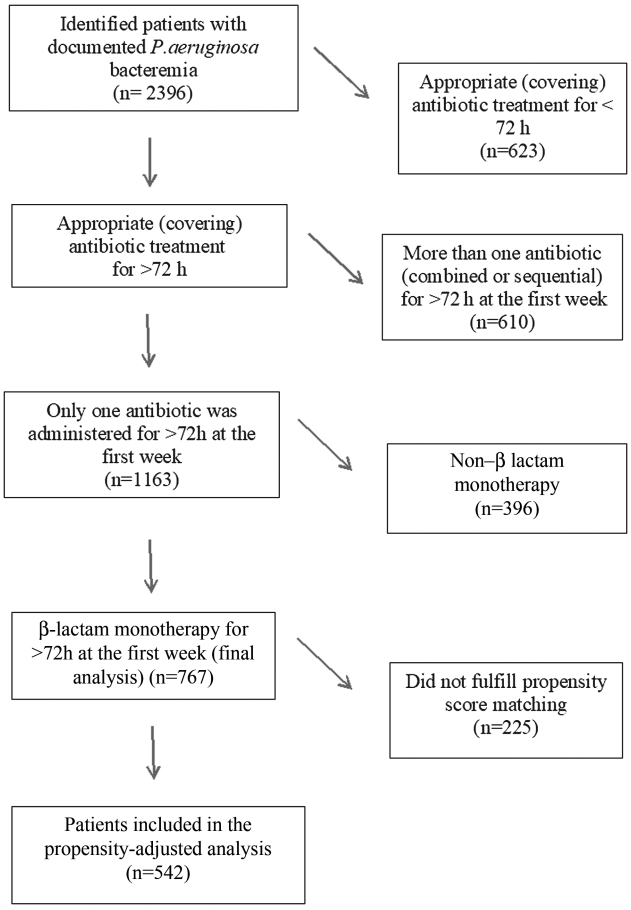

Figure 1. Flowchart of study. Abbreviation: *P. aeruginosa*, *Pseudomonas aeruginosa*.

appropriate empirical therapy vs 15 of 126 [11.9%] patients who died within 30 days; $P = .533$).

Multivariate analyses of risk factors for mortality for both the entire cohort (767 patients) and the propensity score–adjusted cohort (542 patients) are presented in Table 3. The type of definitive monotherapy was not significantly associated with mortality. Significant predictors of mortality in the propensity-matched cohort were functional capacity, bedridden at baseline, higher Charlson comorbidity index, solid metastatic tumor, previous hospitalization within 90 days, nosocomial infection, and higher SOFA score at presentation. Urinary tract source was significantly protective.

Secondary Outcomes Including Adverse Events and Isolation of Strains With New Resistance

Secondary outcomes according to monotherapy type are reported in Table 4. Mortality at day 7 was similar between groups (13/213 [6.1%], ceftazidime; 17/344 [4.9%], piperacillin-tazobactam; 16/210 [7.6%], carbapenems; $P = .435$). No significant difference between groups was demonstrated for the outcomes of clinical or microbiological failure (clinical failure: 78/170 [45.9%], ceftazidime; 114/306 [37.3%], carbapenems; 80/180 [44.4%], piperacillin-tazobactam; $P = .119$; microbiological failure: 23/205 [11.2%], ceftazidime; 31/196 [15.7%], carbapenems; 37/325 [11.4%], piperacillin-tazobactam; $P = .278$).

Late need for respiratory support and late development of septic shock were not significantly different between groups, although a trend for higher rates of late septic shock was apparent in the carbapenem group (14/210 [7%] in the carbapenem group vs 11/213 [5.4%] in the ceftazidime group and 10/344 [3.1%] in the piperacillin-tazobactam group; $P = .110$). Adverse events, including acute kidney injury, diarrhea of any cause, *C. difficile* infection, and seizures, and drug discontinuation due to adverse events were similar between drugs (Table 4).

Concerning isolation of strains with new resistance profile, significantly higher rates of isolation of *P. aeruginosa* strains with new resistance to antipseudomonal drugs were demonstrated with carbapenems (36/206 [17.5%]; imipenem: 12/44 [27.3%]; meropenem: 24/162 [14.8%]) versus ceftazidime (25/201 [12.4%]) and piperacillin-tazobactam (28/332 [8.4%]) ($P = .007$). A summary of baseline susceptibility of *P. aeruginosa* isolates to the β-lactam drugs is presented in Supplementary Table 2. Resistance emergence rates among other gram-negative pathogens or among gram-positive pathogens were not significantly different between drugs.

Duration of hospitalization among patients alive at day 30 was similar between drugs, although duration of fever was longer among patients receiving carbapenems, without reaching statistical significance.

DISCUSSION

In this multinational, multicenter study including 767 patients treated with definitive β-lactam monotherapy for *P. aeruginosa* bacteremia we could not find differences between ceftazidime, carbapenems, and piperacillin-tazobactam in terms of mortality, clinical failure, microbiological failure, or adverse events. Isolation of *P. aeruginosa* with new resistance to antipseudomonal drugs was significantly more common following treatment with carbapenems (36/206 [17.5%]) versus ceftazidime (25/201 [12.4%]) and piperacillin-tazobactam (28/332 [8.4%]) ($P = .007$). Predictors of 30-day mortality evaluated in a multivariate analysis included mainly baseline conditions: bedridden patients, solid metastatic tumor and higher comorbidity index, previous hospitalization within 90 days, and nosocomial acquisition of infection. SOFA score at presentation was also a significant predictor for mortality while urinary tract as the source of bacteremia was a protective factor. The type of β-lactam monotherapy did not affect mortality.

We chose to compare specifically these 3 β-lactams because these are the most commonly used antibiotic for *P. aeruginosa* bacteremia (see Supplementary Table 1) and thus merit a comparison. Previous studies directly comparing

Table 2. Risk Factors for 30-day All-cause Mortality (Univariate Analysis)

Variable	Alive: 30 Days (n = 633)	Dead: 30 Days (n = 134)	*P*
Age, y	68 (57–78)	69.5 (60–79)	.22
Weight (N = 457), kg	72 (62–83.7)	69.35 (59.75–83)	.297
Height (N = 415), m	1.7 ± 0.09	1.67 ± 0.09	.025
Female gender, n (%)	196 (31)	49 (36.6)	.206
Department at time of culture collection—ICU, n (%)	94 (14.9)	33 (24.6)	.006
Bedridden at baseline, n/N (%)	21/581 (3.6)	15 /126 (11.9)	<.01
Arrival from home, n/N (%)	526/632 (83.2)	108/133 (81.2)	.651
Previous hospitalization (90 days), n/N (%)	343/625 (54.9)	85/131 (64.9)	.036
Endotracheal tube, n (%)	61 (9.6)	32 (23.9)	.000
Arterial line, n (%)	72 (11.4)	23 (17.3)	.061
Central venous line, n (%)	252 (39.9)	62 (46.6)	.155
Nasogastric tube, n (%)	84 (14.4)	40 (31.7)	.000
Urinary catheter, n (%)	236 (37.3)	70 (52.6)	.001
Any other foreign device,[a] n (%)	132 (20.9)	30 (22.6)	.668
Chemotherapy previous 30 days, n (%)	165 (26.1)	41 (30.6)	.287
Steroid therapy,[b] n (%)	108 (17.1)	32 (24.1)	.06
Previous surgery (30 days), n (%)	175 (27.6)	36 (26.9)	.854
Chronic dialysis, n (%)	33 (5.2)	5 (3.8)	.478
Intravenous drug use, n (%)	11 (1.7)	7 (5.2)	.016
Neutropenia, n (%)	119 (18.8)	28 (20.9)	.575
Charlson score	3 (1–6)	4 (2–7)	.035
Charlson score components, n (%)			
Congestive heart failure	99 (15.6)	24 (17.9)	.515
Solid metastatic tumor	72 (11.4)	35 (26.1)	.000
Hemiplegia/hemiparesis	40 (6.3)	9 (6.7)	.864
Diabetic end organ	81 (12.8)	14 (10.4)	.453
Dementia	36 (5.7)	9 (6.7)	.645
Severe renal failure	81 (12.8)	24 (17.9)	.118
Chronic pulmonary disease	90 (14.2)	26 (19.4)	.128
Mild liver disease	30 (4.7)	6 (4.5)	.896
Moderate–severe liver disease	16 (2.5)	8 (6)	.038
Rheumatic	51 (8.1)	9 (6.7)	.6
Any malignancy	252 (39.8)	56 (41.8)	.671
Hospital-acquired infection	309 (48.8)	84 (62.7)	.004
MDR *Pseudomonas*	41 (6.5)	17 (12.7)	.014
Sepsis presentation			
Urinary source, n (%)	167 (26.4)	18 (13.4)	<.01
Pulmonary source, n (%)	82 (13)	30 (22.4)	<.01
Temperature (N = 736), °C	38.52 ± 0.98	38.33 ± 1.11	.07
Heart rate (N = 661)	104.81 ± 22.35	111.27 ± 22.48	<.01
Systolic blood pressure (N = 726)	103.8 ± 23.82	95.5 ± 21.4	<.01
Diastolic blood pressure (N = 667)	58 (50–65)	52 (45–61)	<.01
Leukocytes (N = 742), $\times 10^9$ /L	11 (3.11–18.1)	9 (3.11–16.45)	.684
Albumin (N = 476), g/dL	2.7 (2.3–3.2)	2.3 (1.8–2.8)	<.01
Creatinine (N = 739), mg/dL	1.14 (0.77–1.82)	1.16 (0.77–2.23)	.683
Sepsis management			
Inappropriate empirical treatment (<48 hours), n/N (%)	80/571 (14)	15/126 (11.9)	.533
Definitive monotherapy			.483
Ceftazidime, n (%)	176 (27.8)	37 (27.6)	
Carbapenem, n (%)	168 (26.5)	42 (31.3)	
Piperacillin-tazobactam, n (%)	289 (45.7)	55 (41)	
Way of administration—intermittent,[c] n/N (%)	524/627 (83.6)	109/133 (82)	.650
Maximal dose administered,[d] n/N (%)	239/591 (40.4)	44/127 (34.6)	.225

Continuous variables are presented as median (IQR) or mean ± SD according to distribution of variable; categorical variables are presented as no. (%).
Abbreviations: ICU, intensive care unit; IQR, interquartile range; MDR, multidrug resistance; SD, standard deviation.

[a]Any other foreign device, including prosthetic joint, prosthetic valve, implantable cardiovascular device or vascular graft.

[b]Steroid therapy: defined as 10 mg prednisone or equivalent daily for more than 30 consecutive days.

[c]Intermittent administration of antibiotics as opposed to extended or continuous.
[d]Definitions of maximal doses of definitive antibiotics are presented in Appendix 2.

Table 3. Multivariate Analyses for Risk Factors for 30-day All-cause Mortality: Entire Cohort and Propensity Score–Adjusted Cohort

Variable	Odds Ratio (95% CI)		
	Univariate Analysis	Multivariate Logistic Regression Analysis (n = 767)	Multivariate Logistic Regression Analysis, Propensity Score Adjusted (n = 542)
Definitive treatment (carbapenem as reference)			
Ceftazidime	0.84 (.52–1.37)	0.92 (.5–1.67)	1.14 (.52–2.46)
Piperacillin-tazobactam	0.76 (.48–1.18)	1.17 (.69–1.67)	1.3 (.67–2.51)
Hospital-acquired infection	1.76 (1.2–2.58)	1.56 (.94–2.57)	2.16 (1.12–4.18)
Nasogastric tube	2.76 (1.78–4.29)	1.98 (1.04–3.75)	1.8 (.72–4.48)
Bedridden at baseline	3.6 (1.8–7.21)	3.18 (1.37–7.39)	3.99 (1.52–10.53)
Urinary catheter	1.86 (1.28–2.72)	1.2 (.7–2.07)	1.32 (.67–2.61)
Intravenous drug use	3.1 (1.18–8.15)	3.06 (.73–12.83)	…
Solid metastatic tumor	2.75 (1.74–4.35)	3.75 (2.15–6.54)	3.25 (1.61–6.6)
Urinary source	0.433 (.26–.73)	0.48 (.25–.89)	0.34 (.15–.76)
Previous hospitalization (90 days)	0.96 (.63–1.46)	1.46 (.93–2.31)	1.92 (1.02–3.6)
Charlson score	1.06 (1.004–1.13)	1.1 (1.02–1.19)	1.11 (1.001–1.23)
Systolic blood pressure	0.98 (.96–.99)	0.99 (.98–1.001)	0.99 (.98–1.003)
SOFA score	1.23 (1.15–1.31)	1.23 (1.15–1.32)	1.19 (1.07–1.32)

Hospital was introduced as a random-effect variable, goodness of fit - quasi-likelihood under the independence model criterion (QIC) – 610.73 constant β = –0.539. The following variables were not introduced into the multivariate analysis due to significant correlation or causal connection with other variables (endotracheal tube, MDR pseudomonas, and diastolic blood pressure).
Abbreviations: CI, confidence interval; MDR, multidrug resistance; SOFA, sequential organ failure assessment.

different monotherapies for *P. aeruginosa* bacteremia were small studies, demonstrating no significant difference in clinical outcomes between the various antibiotics. Tan et al [11] evaluated 69 patients treated with ceftazidime, carbapenems, or piperacillin-tazobactam for *P. aeruginosa* bacteremia. No significant difference in mortality was demonstrated between monotherapies in this study. A similar comparison was conducted in another retrospective study including 131 patients and demonstrated no significant association between type of monotherapy and 30-day mortality [12]. A third retrospective study compared the 3 drug groups among 103 patients with *P. aeruginosa* bacteremia, although 25% of patients received combination therapy. No significant difference was demonstrated in terms of mortality and clinical cure; however, microbiological cure was significantly lower with piperacillin-tazobactam [13]. The explanation suggested for the lower microbiological cure with piperacillin-tazobactam was a lower probability of achieving a high percentage of time above the minimal inhibitory concentration (MIC) with piperacillin-tazobactam compared with the other β-lactams [13]. This lower microbiological cure with piperacillin-tazobactam was not demonstrated in our cohort.

Our finding of higher rates of isolates with newly documented resistance to antipseudomonal drugs following carbapenem therapy, and specifically imipenem, has been previously described. A systematic review comparing imipenem versus other regimens for pneumonia caused by *P. aeruginosa* demonstrated higher rates of resistance emergence to imipenem during treatment, with resistance to imipenem developing in 38.7% of *P. aeruginosa* isolates versus 21.9% in the comparator treatment group [14]. Similar rates of rapid resistance emergence to carbapenems among *P. aeruginosa*–infected patients were reported in additional studies [27, 28]. This finding, however, is limited by our definition of new resistance, as it could be resistance to any antipseudomonal drug rather than to the antibiotic used. We therefore cannot differentiate whether these cases are resistance emergence in the same strain or new infections with a different strain.

Several studies reviewed risk factors for mortality in patients with *P. aeruginosa* bacteremia with variable findings. Similar to our results, lower functional capacity [29], severity of infection presentation scores [30, 31], and severe comorbidities [11, 32] were all described as risk factors for mortality.

Our study is the largest to date comparing various β-lactam monotherapies for the definitive treatment of *P. aeruginosa* bacteremia, including data from 25 centers in 9 countries. Limitations first include the retrospective data collection. Although a propensity score analysis was used, residual bias in baseline characteristics of patients may have remained. No significant difference in mortality was demonstrated between the investigated drugs; however, the wide confidence intervals demonstrated for this outcome in the propensity-adjusted cohort in addition to the risk of residual confounding by indication warrant a randomized controlled trial. In addition, mortality rates in our cohort are lower than those documented for *P. aeruginosa* bacteremia in previous studies. The explanation for the lower mortality is probably the inclusion of patients receiving definitive therapy for at least 72 hours, thus excluding patients with early death. The comparison was only between β-lactams. We assumed fluoroquinolone monotherapy is saved for patients with milder illness. Since we focused on definitive

Table 4. Secondary Outcomes According to Drug Group

Outcome	Ceftazidime (n = 213)	Piperacillin-Tazobactam (n = 344)	Carbapenem (n = 210)	Total Cohort (n = 767)	*P*
Clinical outcomes					
7-day mortality, n (%)	13 (6.1)	17 (4.9)	16 (7.6)	46 (6)	.435
Clinical failure, n/N (%)	78/170 (45.9)	114/306 (37.3)	80/180 (44.4)	272/656 (41.5)	.119
Late septic shock, n (%)	11 (5.4)	10 (3.1)	14 (7)	35 (4.8)	.110
Late need for respiratory support, n (%)	11 (5.6)	8 (2.5)	10 (5.1)	29 (4.1)	.167
Hospital duration, days					
Entire cohort (N = 721)	13 (9–23)	13 (7–24)	14 (8–28)	13 (8–24)	.363
Alive at day 30 (N = 587)	14 (9–31)	13 (8–27.5)	15 (9–38)	14 (9–31)	.16
Microbiological failure (N = 727), n/N (%)	23/205 (11.2)	37/325 (11.4)	31/196 (15.7)	91/723 (12.5)	.278
Fever duration, days					
Entire cohort (N = 641)	1 (1–3)	1 (0.75–3)	1 (1–4)	1 (1–3)	.14
Alive at day 30 (N = 526)	1 (1–3)	1 (1–2)	2 (1–4)	1 (1–3)	.094
Adverse events					
Renal failure, n (%)	(N = 195)	(N = 334)	(N = 209)	(N = 738)	.217
No	169 (86.7)	289 (86.5)	181 (86.6)	639 (86.6)	
Risk	14 (7.2)	22 (6.6)	8 (3.8)	44 (6)	
Injury	6 (3.1)	8 (2.4)	6 (2.9)	20 (2.7)	
Failure	0	7 (2.1)	9 (4.3)	16 (2.2)	
Loss	3 (1.5)	2 (0.6)	3 (1.4)	8 (1.1)	
ESKD, n (%)	3 (1.5)	6 (1.8)	2 (1)	11 (1.5)	
Any diarrhea, n/N (%)	26/204 (12.7)	55/333 (16.5)	26/209 (12.4)	107/746 (14.3)	.313
Clostridium difficile infection, n/N (%)	3/205 (1.5)	8/339 (2.4)	2/209 (1)	13/753 (1.7)	.446
Anaphylactic shock	0	0	0	0	
Any rash, n/N (%)	4/190 (2.1)	9/330 (2.7)	4/207 (1.9)	17/727 (2.3)	.813
Seizures, n/N (%)	4/191 (2.1)	5/330 (1.5)	1/207 (0.5)	10/728 (1.4)	.369
Drug discontinuation due to adverse events, n/N (%)	2/191 (1)	3/330 (0.9)	4/207 (1.9)	9/728 (1.2)	.558
New resistance profile, n/N (%)					
Resistant PA	25/201 (12.4)	28/332 (8.4)	36/206 (17.5)	89/739 (12)	.007
Resistant GNRs[a]	15/204 (7.4)	29/333 (8.7)	22/206 (10.7)	66/743 (8.9)	.491
MRSA	6/200 (3)	7/323 (2.2)	4/205 (2)	17/728 (2.3)	.756
VRE	3/202 (1.5)	4/323 (1.2)	5/206 (2.4)	12/731 (1.6)	.565

Continuous variables are presented as median (IQR) or mean ± SD according to distribution of variable; categorical variables are presented as no. (%). Definitions of secondary outcomes, including new resistance profile are presented in Appendix 3.

Abbreviations: ESKD, end-stage kidney disease; IQR, interquartile range; GNR, gram-negative rod; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; SD, standard deviation; VRE, vancomycin-resistant enterococci.

[a]Gram-negative bacteria other than *Pseudomonas*.

therapy we cannot make recommendations concerning empirical therapy. These are related to local susceptibility patterns and stewardship indications.

In conclusion, among β-lactam drugs used as monotherapy for the treatment of *P. aeruginosa* bacteremia, no significant difference was demonstrated in terms of mortality, clinical or microbiological failure, and adverse events between the different antibiotics. Higher rates of isolation of *P. aeruginosa* strains with a new resistance profile after treatment with carbapenems suggest a preference of ceftazidime or piperacillin-tazobactam for treating *P. aeruginosa* bacteremia. Local stewardship indications may dictate the choice between these 2 drugs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. T. B., D. Y., L. L., P. N., and M. P. conceived of and designed the study. T. B., D. Y., and L. L. wrote the protocol and developed the database. All authors participated in data collection. T. B., D. Y., P. N., J. K. V., C. G. G., C. P., R. B. A., L. N., E. T., J. R.-B., A. O., E. R. d. G., A. C., B. B., L. P., M. P., and L. L. analyzed and interpreted data. All authors contributed to the writing or critical revision of the final manuscript.

Acknowledgments. The authors thank the following for their assistance in the manuscript: Alain Lozniewski (Nancy, France), Thibault Mansuy (Nancy, France), Assaf Halavie (Petah-Tikva, Israel), Lia Koren (Petah-Tikva, Israel). This work was performed in partial fulfillment of the requirements for a PhD degree of Tanya Babich, Sackler Faculty of Medicine, Tel Aviv University, Israel. This study was presented as poster presentation at the European Society of Clinical Microbiology and Infectious Diseases annual conference, Madrid, Spain, 21–24 April 2018.

Financial support. This study was conducted with no external funding. In Sweden only, the research was funded by grants from the Stockholm County Council and Emil and Wera Cornell Foundation.

Potential conflicts of interest. The authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
2. Ammerlaan HS, Harbarth S, Buiting AG, et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. Clin Infect Dis **2013**; 56:798–805.
3. Horino T, Chiba A, Kawano S, et al. Clinical characteristics and risk factors for mortality in patients with bacteremia caused by *Pseudomonas aeruginosa*. Intern Med **2012**; 51:59–64.
4. Kang CI, Kim SH, Kim HB, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. Clin Infect Dis **2003**; 37:745–51.
5. Cheong HS, Kang CI, Wi YM, et al. Inappropriate initial antimicrobial therapy as a risk factor for mortality in patients with community-onset *Pseudomonas aeruginosa* bacteraemia. Eur J Clin Microbiol Infect Dis **2008**; 27:1219–25.
6. Dantas RC, Ferreira ML, Gontijo-Filho PP, Ribas RM. *Pseudomonas aeruginosa* bacteraemia: independent risk factors for mortality and impact of resistance on outcome. J Med Microbiol **2014**; 63:1679–87.
7. Vitkauskienė A, Skrodenienė E, Dambrauskienė A, Macas A, Sakalauskas R. *Pseudomonas aeruginosa* bacteremia: resistance to antibiotics, risk factors, and patient mortality. Medicina (Kaunas) **2010**; 46:490–5.
8. Peña C, Suarez C, Ocampo-Sosa A, et al; Spanish Network for Research in Infectious Diseases (REIPI). Effect of adequate single-drug vs combination antimicrobial therapy on mortality in *Pseudomonas aeruginosa* bloodstream infections: a post hoc analysis of a prospective cohort. Clin Infect Dis **2013**; 57:208–16.
9. Paul M, Leibovici L. Combination therapy for *Pseudomonas aeruginosa* bacteremia: where do we stand [editorial commentary]? Clin Infect Dis **2013**; 57:217–20.
10. Vardakas KZ, Tansarli GS, Bliziotis IA, Falagas ME. β-Lactam plus aminoglycoside or fluoroquinolone combination versus β-lactam monotherapy for *Pseudomonas aeruginosa* infections: a meta-analysis. Int J Antimicrob Agents **2013**; 41:301–10.
11. Tan SH, Teng CB, Ng TM, Lye DC. Antibiotic therapy and clinical outcomes of *Pseudomonas aeruginosa* (PA) bacteraemia. Ann Acad Med Singapore **2014**; 43:526–34.
12. Paulsson M, Granrot A, Ahl J, et al. Antimicrobial combination treatment including ciprofloxacin decreased the mortality rate of *Pseudomonas aeruginosa* bacteraemia: a retrospective cohort study. Eur J Clin Microbiol Infect Dis **2017**; 36:1187–96.
13. Kwee F, Walker SA, Elligsen M, Palmay L, Simor A, Daneman N. Outcomes in documented *Pseudomonas aeruginosa* bacteremia treated with intermittent IV infusion of ceftazidime, meropenem, or piperacillin-tazobactam: a retrospective study. Can J Hosp Pharm **2015**; 68:386–94.
14. Zilberberg MD, Chen J, Mody SH, Ramsey AM, Shorr AF. Imipenem resistance of *Pseudomonas* in pneumonia: a systematic literature review. BMC Pulm Med **2010**; 10:45.
15. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis **2016**; 63:e61–111.
16. Torres A, Niederman MS, Chastre J, et al. Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J. **2017**; 50:1–26.
17. Diallo K, Thilly N, Luc A, et al; European Study Group for Antimicrobial Stewardship European Study Group for Bloodstream Infections, Endocarditis and Sepsis. Management of bloodstream infections by infection specialists: an international ESCMID cross-sectional survey. Int J Antimicrob Agents **2018**; 51:794–8.
18. Papst L, Beović B, Pulcini C, et al. Antibiotic treatment of infections caused by carbapenem-resistant gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals. Clin Microbiol Infect. **2018**; pii: S1198-743X(18)30069-7.
19. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother **2008**; 52:1028–33.
20. Kwak YG, Choi SH, Choo EJ, et al. Risk factors for the acquisition of carbapenem-resistant *Klebsiella pneumoniae* among hospitalized patients. Microb Drug Resist **2005**; 11:165–9.
21. Shiber S, Yahav D, Avni T, Leibovici L, Paul M. β-Lactam/β-lactamase inhibitors versus carbapenems for the treatment of sepsis: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother **2015**; 70:41–7.
22. Lee SO, Lee ES, Park SY, Kim SY, Seo YH, Cho YK. Reduced use of third-generation cephalosporins decreases the acquisition of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol **2004**; 25:832–7.
23. Hill DA, Herford T, Parratt D. Antibiotic usage and methicillin-resistant *Staphylococcus aureus*: an analysis of causality. J Antimicrob Chemother **1998**; 42:676–7.
24. Nasiri MJ, Goudarzi M, Hajikhani B, Ghazi M, Goudarzi H, Pouriran R. *Clostridium difficile* infection in hospitalized patients with antibiotic-associated diarrhea: a systematic review and meta-analysis. Anaerobe **2018**; 50:32–7.
25. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ **2009**; 338:b2393.
26. Spreeuwenberg MD, Bartak A, Croon MA, et al. The multiple propensity score as control for bias in the comparison of more than two treatment arms: an introduction from a case study in mental health. Med Care **2010**; 48:166–74.
27. Zou Y, Lian J, Di Y, et al. The quick loss of carbapenem susceptibility in *Pseudomonas aeruginosa* at intensive care units. Int J Clin Pharm **2018**; 40:175–82.
28. Yusuf E, Van Herendael B, Verbrugghe W, et al. Emergence of antimicrobial resistance to *Pseudomonas aeruginosa* in the intensive care unit: association with the duration of antibiotic exposure and mode of administration. Ann Intensive Care **2017**; 7:72.
29. Schechner V, Gottesman T, Schwartz O, et al. *Pseudomonas aeruginosa* bacteremia upon hospital admission: risk factors for mortality and influence of inadequate empirical antimicrobial therapy. Diagn Microbiol Infect Dis **2011**; 71:38–45.
30. Hirsch EB, Cottreau JM, Chang KT, Caeiro JP, Johnson ML, Tam VH. A model to predict mortality following *Pseudomonas aeruginosa* bacteremia. Diagn Microbiol Infect Dis **2012**; 72:97–102.
31. Yoon YK, Kim HA, Ryu SY, et al; Antibiotic Stewardship Study Group. Tree-structured survival analysis of patients with *Pseudomonas aeruginosa* bacteremia: a multicenter observational cohort study. Diagn Microbiol Infect Dis **2017**; 87:180–7.
32. Joo EJ, Kang CI, Ha YE, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. Microb Drug Resist **2011**; 17:305–12.

APPENDIX 1: List of Antipseudomonal Drugs

1. Antipseudomonal penicillins
   a. Ticarcillin
   b. Piperacillin

   Both alone or in combination with a β-lactamase inhibitor:
   a. Ticarcillin-clavulanate
   b. Piperacillin-tazobactam
2. Cephalosporins
   a. Ceftazidime
   b. Cefepime
3. Monobactams
   a. Aztreonam
4. Fluoroquinolones
   a. Ciprofloxacin
   b. Ofloxacin
   c. Levofloxacin
5. Carbapenems
   a. Meropenem
   b. Doripenem
   c. Imipenem
6. Aminoglycosides
   a. Gentamicin
   b. Tobramycin
   c. Amikacin
7. Polymyxins
   a. Colistin
   b. Intravenous fosfomycin

APPENDIX 2: Definitions of Maximal Dose by Drug According to Renal Function

Creatinine Clearance, mL/min	Dose	Units	Times Daily
Meropenem			
>50	2	Gram	3
26–50	2	Gram	2
10–25	1	Gram	2
<10	1	Gram	1
Intermittent hemodialysis	1	Gram	1
Peritoneal dialysis	1	Gram	1
CRRT	2	Gram	2
Imipenem			
>50	0.5	Gram	4
10–50	0.25	Gram	3
<10	0.25	Gram	2
Intermittent hemodialysis	0.25	Gram	2
Peritoneal dialysis	0.25	Gram	2
CRRT	1	Gram	2
Ceftazidime			
>50	2	Gram	3
10–50	2	Gram	2
<10	2	Gram	1
Intermittent hemodialysis	2	Gram	1
Peritoneal dialysis	0.5	Gram	1
CRRT	1.25	Gram	3
Piperacillin- tazobactam			
>40	4.5	Gram	4
20–40	3.375	Gram	4
<20	2.25	Gram	4
Intermittent hemodialysis	2.25	Gram	3
Peritoneal dialysis	2.25	Gram	3
CRRT	3.375	Gram	4

Abbreviation: CCRT, continuous renal replacement therapy.

APPENDIX 3: DEFINITIONS OF SECONDARY OUTCOMES

Clinical failure, defined as failure to achieve clinical stability (temperature <38°C, blood pressure within normal ranges without vasopressor treatment, saturation >90% or as baseline without respiratory support and alive) at day 7. (Blood pressure within normal ranges = systolic blood pressure >90 mmHg and mean arterial pressure > 70 mmHg.)

Microbiological failure, defined as the persistence or re-isolation of the same bacteria/phenotype (as determined by the antibiotic susceptibility profile if bacteria not identified) in blood 48 hours or more after definitive treatment initiation and within 30 days of index infection.

Late septic shock, defined as septic shock that developed 48 hours or more and within 1 week after start of appropriate antibiotic treatment.

Late need for respiratory support, defined as need for respiratory support that developed 48 hours or more and within 1 week after start of appropriate antibiotic treatment.

Fever duration: defined as the number of days in which a temperature ≥38°C is documented from start of appropriate treatment until 2 consecutive days without fever (<38°C).

Duration of hospitalization since the onset of bacteremia.

Isolation of strains with new resistance profile within 30 days from definitive treatment start. Including the following:

a. Isolation of *P. aeruginosa* (colonization or infection) of any site with new resistance that was not apparent in the original isolate to any of the followings within 30 days: aminoglycosides, carbapenems, ceftazidime, antipseudomonal penicillins, or fluoroquinolones.
b. Isolation of any other gram-negative bacteria (colonization or infection) resistant to any antipseudomonal drug within 30 days.
c. Isolation of MRSA (colonization or infection) within 30 days.
d. Isolation of vancomycin-resistant enterococci (colonization or infection) within 30 days.

- Adverse events during 30 days from blood culture collection (or until discharge/death):
  - renal failure, defined using the RIFLE criteria;
  - diarrhea (any);
  - *Clostridium difficile*–associated diarrhea (according to positive antigen plus toxin assay or positive polymerase chain reaction assay or compatible findings on endoscopy);
  - anaphylactic shock;
  - any rash;
  - seizures;
  - drug discontinuation due to adverse event.