International Journal of Antimicrobial Agents 54 (2019) 716–722

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Clinical predictors and outcome impact of community-onset polymicrobial bloodstream infection

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ARTICLE INFO

Article history:
Received 16 March 2019

Editor: Jason Roberts

Keywords:
Bacteraemia
Emergency department
Epidemiology
Polymicrobial bloodstream infection
Risk factors
Sepsis

ABSTRACT

Objectives: Very few studies have characterised community-onset polymicrobial bloodstream infections (BSIs). This study determined the incidence, risk factors, and outcomes of polymicrobial BSI as compared with monomicrobial BSI in a cohort of patients with community-onset BSIs.

Methods: This prospective cohort study enrolled consecutive patients with laboratory confirmed BSIs who were admitted to two tertiary emergency departments in Taiwan between 1 January 2015 and 31 December 2016. It assessed the independent impact of polymicrobial BSIs on survival by a propensity score weighting method. Subsequently, independent clinical predictors were identified with multivariate logistic regression model analysis with internal validation by 10-fold cross validation.

Results: Among 1166 patients with community-onset BSI, 133 (10.9%) episodes of polymicrobial BSIs occurred. Anaerobe, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus* spp., and *Candida* spp. were the most common isolated microorganisms in polymicrobial BSI. Polymicrobial BSIs were associated with an increased 90-day mortality rate (OR 2.20, 95% CI 1.98–2.60). A prediction model was built to predict polymicrobial BSI with moderate predictability (c statistic = 0.78). Significant predictors included biliary tract infection, nosocomial infection, nursing home residence, stroke, and afebrile presentation.

Conclusions: Polymicrobial BSI occurred in approximately 1 in 10 episodes of community-onset BSI and was independently associated with excess mortality. Clinical predictors identified in this study may help guide the prescription of empiric broad-spectrum antibiotics.

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Introduction

Bloodstream infection (BSI) is a major cause of morbidity and mortality worldwide, with an estimated annual incidence of 575 000–677 000 and resultant deaths of 79 000–94 000 in North America each year [1]. The mortality rate of community-acquired BSI varies across different reports, ranging from 4–16% for community-onset BSI and 14–28% for hospital-acquired BSI [1–5,36,37]. Besides short-term morbidity and mortality, BSI has also been shown to increase late mortality beyond 1 month of presentation [6].

The incidence of polymicrobial BSI, defined as the discovery of the presence of more than two different microorganisms in blood culture, has been rising for the past decades. Probable causes include an aging population, prolonged lives of patients with cancer, haematological diseases, multiple comorbidities, or immunocompromised conditions. Several studies have reported on the epidemiology of polymicrobial BSI [5,7–14]. These studies were mostly performed on patients with hospital-acquired BSI with

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https://doi.org/10.1016/j.ijantimicag.2019.09.015
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underlying malignancy, transplantation status, or immunocompromised status. They showed that inappropriate initial antibiotic therapy and an absence of fever were predictors for mortality [13,15–19]. However, reports on the bacteriology, clinical predictors, and outcome impact of community-acquired polymicrobial BSI in an emergency department (ED) setting are rare, which is the main route of admission for patients with a community-onset BSI. Therefore, identifying significant clinical predictors and common pathogens of community-onset polymicrobial BSI at an ED may be important to guide timely and effective use of broader spectrum or combination antibiotics in suspected patients.

Timely and effective antibiotic treatment is crucial to the survival of BSI patients; however, blood culture results are usually not available until 48–72 hours after initial presentation. In recent reports, as many as 50% of patients with polymicrobial BSI did not receive appropriate initial antibiotics, underscoring the importance of clinical knowledge of bacteriology and clinical predictors. Most previous studies are old and were conducted in intensive care unit settings [7,8,10,11,14,16,20]. The one study performed in an ED did not address the clinical characteristics and outcome of polymicrobial BSI. In addition, no studies have evaluated the clinical predictors of polymicrobial BSI.

In order to address this problem, a prospective cohort study was performed that enrolled continual ED patients with a documented BSI. It compared the clinical characteristics, bacteriology, and outcomes between patients with polymicrobial and monomicrobial BSI. The specific aim was three-fold: 1) to characterise patients with community-onset polymicrobial BSI and identify independent clinical predictors that are readily available in the ED setting; 2) to characterise the bacteriology profile associated with community-onset polymicrobial BSI; 3) to determine the independent survival impact of polymicrobial BSI as compared with monomicrobial BSI.

Study design and setting

Patient cohort

This study was prospectively conducted at the National Taiwan University Hospital Yunlin Branch between 1 January 2015 and 31 December 2016. The National Taiwan University Hospital Yunlin branch comprises two hospitals in two cities of Yunlin counties. The primary hospital in Douliou city is a 941-bed primary and tertiary care hospital with an annual ED census in excess of 50 000 visits. The secondary hospital in Huwei city is a 217-bed primary and secondary care hospital with an annual ED census in excess of 10 000 visits. The source population consisted of all patients aged $\geq$ 20 years admitted to the two EDs during the study period, and for whom blood cultures were obtained with clinical signs of sepsis or with clinical indications of systemic infection. Sepsis was defined by the systemic inflammatory response syndrome (SIRS) criteria [38]. Clinical signs of systemic inflammatory response syndrome include temperature, pulse rate, respiratory rate, and white blood cell count. Patients were followed for at least 90 days, including the hospital course and clinic visits after discharge, and/or telephone interview.

Laboratory tests

Two sets of blood cultures with one set of aerobic and another set of anaerobic blood culture were obtained from patients with clinical signs of systemic infection. Blood cultures were obtained by general venepuncture guidelines to draw no less than 10 mL of blood when possible. Blood was injected into BacT/ALERT (bioMérieux, Marcy-l'Etoile, France) bottles. The positive blood cultures were inoculated on blood agar, and then incubated in an aerobic or anaerobic chamber at 35°C for 48 hours. All isolates were identified by a conventional method.

Clinical information collection

The following data were collected for all eligible patients: demographic characteristics, pre-existing comorbid medical conditions, exposure to indwelling catheters, initial vital signs, routine laboratory test results, need for mechanical ventilation or haemodialysis, admission and final discharge diagnoses, and identity of microorganisms isolated from the blood cultures. Comorbidities were recorded according to the Charlson Comorbidity score. The presence and source of a focal infection was classified by the final discharge diagnosis as lower respiratory tract infection, urinary tract infection, biliary tract infection, skin and musculoskeletal infection, infective endocarditis, liver abscess, spontaneous bacterial peritonitis, other intra-abdomen infection, catheter-related bloodstream infection, or miscellaneous infections. Those without a localised source of bacteria after an extensive admission workup were classified as primary bacteraemia. Polymicrobial bacteraemia was defined as either growth of two or more different species of microorganisms in the same blood culture or growth of different species in two or more separate blood cultures within the same case. Adequate antimicrobial was defined as the use of an antimicrobial agent with in vitro activity and microbiologically effective against the causative pathogen within 12 hours of ED presentation. All data were prospectively collected by a trained study nurse. This study was approved by the Ethical Review Board of National Taiwan University Hospital.

Outcome definition

The outcome of this study was defined as mortality from polymicrobial and monomicrobial BSI, as shown in the Kaplan-Meier Survival Curve of Figure 1.

Statistical analysis

For continuous variables, normality was tested by Shapiro-Wilk test. Variables with normal distribution were presented with mean and standard deviation. Variables with non-normal distribution were presented with median with interquartile range. For categorical variables, absolute and relative frequencies were calculated. For univariate analysis, the groups were compared using the χ^2 test or Fisher exact test, as indicated for categorical variables, and Mann-Whitney U test for continuous variables. Risk factors of polymicrobial BSI were evaluated by multivariable logistic regression model and variables were selected using the backward elimination method. The model discrimination was measured by C-statistics and model fit was tested by Hosmer-Lemeshow χ^2 test. For validation of the predictive model, a 10-fold cross validation was performed. Unlike the data-splitting approach, this approach permits the use of the entire dataset for model development. The optimism-corrected C-statistics were reported. To evaluate the impact of polymicrobial BSI on the outcome of bacteraemia patients, Kaplan-Meier survival curves were first plotted and the survival between patients with polymicrobial and monomicrobial BSI was compared by log-rank test. Given the known differences in patient characteristics between polymicrobial and monomicrobial BSI, inverse probability of treatment weighting (IPTW) using the propensity score (PS) was employed to create weighted samples of individuals with polymicrobial or monomicrobial BSI, where measured baseline covariates were balanced between the two groups [21,22]. A PS for polymicrobial BSI was estimated by developing a logistic regression model with 17 covariates describing patient demographic and characteristics that are known to be associated

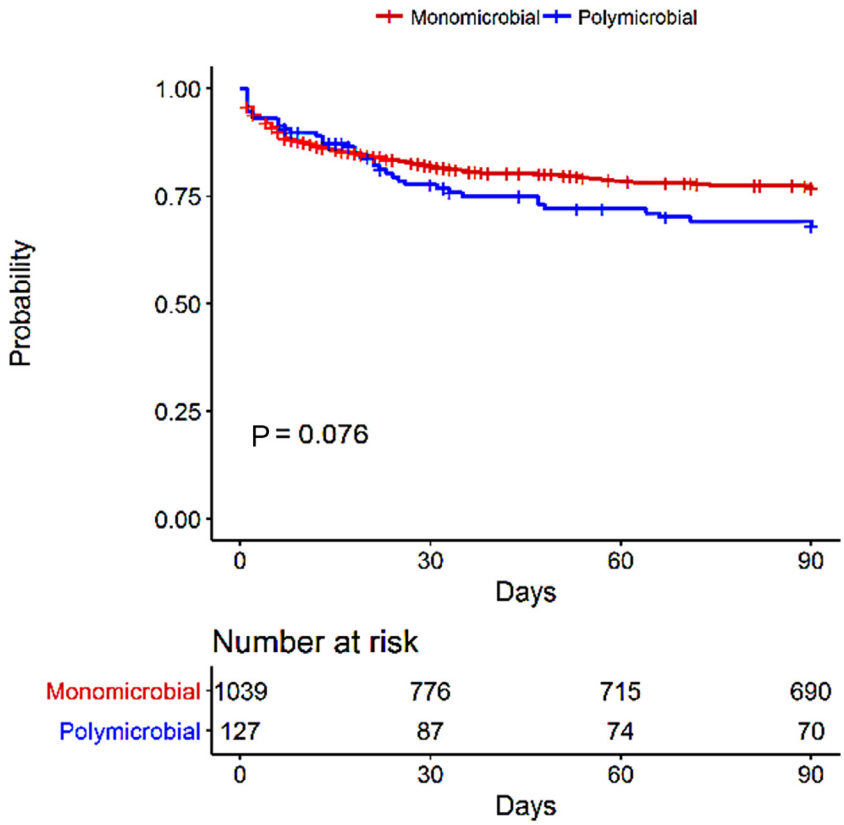

Figure 1. The Kaplan-Meier survival curves show the 90-day survival between patients with polymicrobial vs. monomicrobial bloodstream infection.

with polymicrobial BSI and the outcomes. Odds ratios with 95% confidence intervals and *P*-value were reported. See Supplementary Table 1 for the component variables of the PS model and their corresponding weights. In the IPTW-weighting analysis, the IPTW was used to weight the logistic regression model, and derive an estimate that was independent of the potential confounding effect by all component variables in the PS. Robust sandwich variance estimators were used to derive a valid confidence interval in the IPTW-weighting analysis. All tests were two-tailed, and *P*-values < 0.05 were considered statistically significant. Data were analysed with SAS software (Version 9.4; SAS Inc., Cary, NC).

Results

Study cohort and patient characteristics

During the study period, 1166 patients with documented BSI were enrolled, of which 1039 (89.1%) were monomicrobial BSI and 127 (10.9%) were polymicrobial BSI. The demographic, patient source, and comorbidity between patients with monomicrobial or polymicrobial BSI were compared. Compared with patients with monomicrobial BSI, patients with polymicrobial BSI were older, less likely to be male, more frequently from a hospital referral or were a nursing home resident, and more likely to have stroke and afebrile presentation. The comparison of between-group patient characteristics is summarised in Table 1.

Comparison of bacteriology and source of infection

The most frequently isolated organisms among patients with polymicrobial BSI were *Escherichia coli* (46 isolates, 36.2%), *Klebsiella pneumoniae* (25.2%), and *Pseudomonas aeruginosa* (11.0%) (Table 2). The most commonly isolated Gram-positive organism in patients with polymicrobial BSI was *Enterococcus faecalis* (11 isolates, 8.7%). Compared with monomicrobial BSI, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Aeromonas hydrophila, Klebsiella oxytoca, Citrobacter* spp., *Stenotrophomonas maltophilia, Enterobacter* spp., and *Candida* spp. were more likely isolated in polymicrobial BSI (Table 2). The most common sources of polymicrobial BSI were biliary tract infection (41 patients, 31.3%), followed by pneumonia (25 patients, 19.7%), and urinary tract infection (20 patients, 15.7%). These three infection sites were also more frequently associated with polymicrobial infection (Table 3).

Independent predictors and survival impact

To determine the independent clinical predictors of polymicrobial BSI, all significant predictors in the univariate analysis were entered into the logistic regression model. The backward elimination method ultimately selected biliary tract infection (OR 7.17), hemiparetic stroke (OR 2.24), nursing home residence (OR 3.48), nosocomial infection (OR 2.77), and lack of fever (OR 1.82) as the five significant clinical predictors (Table 4). The C-statistic for the model was 0.73, indicating moderate discrimination. The optimism corrected C-statistic for 10-fold cross validation was 0.70 (95% CI 0.64–0.74). The goodness of fit for the model was tested by the Hosmer-Lemeshow test, which showed a *P*-value of 0.85. The results indicated that there is no statistical difference between the observed and model-predicted probability of polymicrobial BSI. To evaluate the survival impact of polymicrobial BSI, a Kaplan-Meier survival curve was plotted. Polymicrobial BSI was associated with a higher 90-day mortality (44.9%) than monomicrobial BSI (33.6%). Although patients with polymicrobial BSI tended to have a worse outcome, the log-rank test was not significant (Figure 1, $P = 0.076$). The two survival curves crossed early at around 20 days

Table 1
A comparison of demographic characteristics and underlying comorbidities between polymicrobial and monomicrobial bacteraemia.

	Total (n = 1166)	Monomicrobial bacteraemia (n = 1039)	Polymicrobial bacteraemia (n = 127)	*P*-value
Age (years)	63.76 ± 17.1	63.36 ± 17.23	67.07 ± 15.62	**0.021***
Elderly (age ≥ 65)	638 (54.8%)	560 (53.9%)	78 (61.4%)	0.108
Octogenarians (age ≥ 80)	92 (7.9%)	76 (7.3%)	16 (12.6%)	**0.037***
Gender (male)	609 (52.2%)	537 (51.6%)	72 (56.7%)	0.286
Patient source				
Hospital referral	78 (6.7%)	67 (6.4%)	11 (8.7%)	**0.02***
Nursing home residents	43 (3.7%)	33 (3.2%)	10 (7.9%)	**0.008***
Underlying comorbidity				
Diabetes mellitus	386 (33.1%)	348 (33.5%)	38 (29.9%)	0.419
End-stage renal disease	64 (5.5%)	56 (5.4%)	8 (6.3%)	0.671
Liver cirrhosis	132 (11.3%)	121 (11.6%)	11 (8.7%)	0.316
Hemiparetic stroke	147 (12.6%)	119 (11.5%)	28 (22.0%)	**0.001***
Autoimmune disease	33 (2.8%)	29 (2.8%)	4 (3.1%)	0.818
HIV	12 (1.0%)	11 (1.1%)	1 (0.8%)	1.000
Haematogenous malignancy	45 (3.9%)	43 (4.1%)	2 (1.6%)	0.221
Non-haematogenous malignancy	256 (22.0%)	224 (21.6%)	32 (25.2%)	0.960
Indwelling catheter	46 (3.9%)	41 (3.9%)	5 (3.9%)	0.932
Intravenous drug abuser	37 (3.2%)	36 (3.5%)	1 (0.8%)	0.104
Afebrile	242 (20.8%)	206 (19.8%)	36 (28.3%)	**0.025***
Charlson score	2 (0–3)	2 (0–4)	2 (0–3)	0.591

Table 2
A comparison of microbiological findings between polymicrobial and monomicrobial bacteraemic patients.

Bacteriology	Monomicrobial bacteraemia (n = 1039)	Polymicrobial bacteraemia (n = 127)	*P*-value
Anaerobe	42 (4.0%)	24 (18.9%)	< 0.001*
Gram-negative pathogen			
Escherichia coli	329 (31.7%)	46 (36.2%)	0.300
Klebsiella pneumoniae	167 (16.1%)	32 (25.2%)	0.001
Pseudomonas aeruginosa	30 (2.9%)	14 (11.0%)	< 0.001*
Acinetobacter baumannii	17 (1.6%)	12 (9.4%)	< 0.001*
Aeromonas hydrophila	16 (1.5%)	7 (5.5%)	0.013*
Morganella morganii	5 (0.5%)	2 (1.6%)	0.132
Klebsiella oxytoca	8 (0.8%)	7 (5.5%)	< 0.001*
Citrobacter spp.	3 (0.3%)	6 (4.7%)	< 0.001*
Stenotrophomonas maltophilia	2 (0.2%)	6 (4.7%)	< 0.001*
Enterobacter spp.	0 (0.0%)	10 (7.9%)	< 0.001*
Gram-positive pathogen			
Enterococcus faecalis	18 (1.7%)	11 (8.7%)	< 0.001*
Viridans streptococci	21 (2.0%)	4 (3.1%)	1.000
Staphylococcus aureus	97 (9.3%)	12 (9.4%)	0.967
Streptococcus pneumoniae	15 (1.4%)	4 (3.1%)	0.152
Candida spp.	7 (0.7%)	8 (6.3%)	< 0.001

Table 3
Compare source of bacteraemia between polymicrobial and monomicrobial patients.

Source of bacteraemia	Total	Monomicrobial bacteraemia (n = 1039)	Polymicrobial bacteraemia (n = 127)	*P*-value
Primary bacteraemia	191 (16.4%)	175 (16.8)	16 (12.6%)	0.224
Urinary tract infection	297 (25.5%)	227 (26.7%)	20 (15.7%)	**0.008***
Biliary tract infection	165 (13.4%)	115 (11.1%)	41 (32.3%)	**< 0.001***
Pneumonia	159 (13.6%)	134 (12.9%)	25 (19.7%)	0.035*
Skin and musculoskeletal infection	110 (9.4%)	104 (10.0%)	6 (4.7%)	0.054
Intra-abdomen infection	49 (4.2%)	40 (3.8%)	9 (7.1%)	0.086
Catheter-related infection	46 (3.9%)	41 (3.9%)	5 (3.9%)	1.000
Infective endocarditis	47 (4.2%)	44 (4.0%)	3 (2.4%)	0.471
Liver abscess	55 (4.7%)	49 (4.7%)	6 (4.7%)	0.997
Spontaneous bacterial peritonitis	40 (3.4%)	39 (3.8%)	1 (0.8%)	0.083

and the proportionality assumption for a Cox model was not met. Therefore, the IPTW-weighted logistic regression model was performed. The unadjusted odds ratio was nonsignificant (OR 1.37, 95% CI 0.97–1.93). After adjustment of potential confounders by IPTW weighting, polymicrobial BSI was associated with a 2.2-fold (95% CI 1.98–2.60) increased risk of 90-day mortality as compared with patients with monomicrobial BSI (Table 5). The component variable and relative weight of the PS model are shown in Supplemental Table 1.

Discussion

Based on this study, approximately 10.9% of patients with BSI had polymicrobial BSI. Patients with polymicrobial BSI had a mor-

Table 4
Independent predictors for patients with polymicrobial bacteraemia.

Independent risk factors	Odds ratio	95% confidence interval
Biliary tract infection	7.17	4.36–11.78
Hemiparetic stroke	2.24	1.31–3.82
Nursing home residents	3.48	1.27–9.48
Nosocomial infection	2.77	1.18–6.49
Lack of fever	1.82	1.01–3.29

Table 5
Comparison of survival between patients with polymicrobial or monomicrobial blood stream infection. Survival difference was calculated as hazard ratio (HR) in the full cohort. The marginal structural model was used to adjust for the potential confounding between patients with polymicrobial or monomicrobial infection.

	Crude odds ratio	IPTW-adjusted odds ratio
Polymicrobial vs. monomicrobial blood stream infection	1.37 (0.97, 1.93), $P < 0.001$	2.20 (1.98, 2.60), $P < 0.001$

Abbreviation: IPTW, inverse probability of treatment weighting

tality of 31.5% at 30 days and 44.9% at 90 days after ED admission. Biliary tract infection, hemiparetic stroke, nursing home residence, nosocomial infection, and lack of fever were identified as independent predictors for polymicrobial BSI. Patients with polymicrobial BSI had a two-fold risk of hospital mortality as compared with patients with monomicrobial BSI after adjusting for potential confounders.

The prevalence of polymicrobial aetiology in patients with BSI has been reported to be 8–32% [8,9,9,16]. Although biliary tract infection (29.9%), urinary tract infection (18.2%), and pneumonia (14.6%) have been identified as the three main sources of infection for polymicrobial BSI, it must be noted that the yield rate of blood culture may vary with the sources of infection. Pneumonia has been shown to have a lower rate (4–18%) for secondary bacteraemia [23,24]. The prevalence of documented BSI from pneumonia may thus underestimate the burden of polymicrobial infection in lower respiratory tract infection. In addition, the current study found that intra-abdomen infections also tend to grow multiple organisms ($P = 0.086$) and skin and soft-tissue infections tend to be less likely to develop polymicrobial infection ($P = 0.054$); however, this needs to be confirmed in the future through a sufficiently powered study.

As most previous studies have focused on the predictors of short-term mortality, little was known about predictors of polymicrobial BSI. The current study showed that biliary tract infection, hemiparetic stroke, nursing home residence, nosocomial infection, and lack of fever could help clinicians identify patients at risk of polymicrobial BSI, with moderate discrimination (C-statistic = 0.70). It is believed that this set of predictors, although still far from optimal, are now the only indicators that clinicians can use to identify patients at risk of polymicrobial BSI at the initial encounter. Adequacy of initial empiric antibiotics has consistently been shown to be a critical factor for survival in patients with BSI [25]. Recent technological innovation has made rapid microbiology identification possible. For example, the use of matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) considerably reduces the timeframe required from the initial blood culture positivity to complete bacterial identification. In many centres equipped with MALDI-TOF MS, the turnaround time of the blood culture results is around 18–30 hours [26,27]. Nevertheless, it has to be noted that MALDI-TOF MS has limited discrimination in simultaneously identifying multiple pathogens [28]. Another technology – multiplex PCR – could only identify common pathogens in the multiplex panel and could not reliably identify polymicrobial BSIs [29,30].

Consistent with previous findings, the current study found that polymicrobial BSIs are associated with anaerobes and high-risk bacteria for multi-drug resistance such as *Acinetobacter baumannii, Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Enterococcus faecalis*. In addition, *Candida* spp. has a higher occurrence in polymicrobial BSI than in monomicrobial BSI. Therefore, in patients with suspected polymicrobial BSI who do not respond to initial treatment, coverage for Gram-negative pathogens, including *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, Gram-positive pathogens (especially *Enterococcus* spp.), and anaerobes should be considered. Additional antifungal agents may be considered if the condition keeps deteriorating. It must be also noted the broad spectrum of antibiotics should be quickly de-escalated after the specific pathogen has been identified. Although combination antibiotic treatment is recommended for patients with suspected polymicrobial infection, recent studies comparing combination therapy with monotherapy as the empirical antibiotic regimen for severe sepsis or septic shock have shown conflicting results. A large propensity score matched study showed a favourable outcome for combination therapy, whereas a large randomised trial comparing meropenem plus moxifloxacin to meropenem monotherapy failed to show any benefit [31,32]. The conflicting results were recently explained by a pharmacokinetic/pharmacodynamic difference. Time-dependent antibiotics, such as extended penicillin (e.g., ampicillin, ticarcillin, piperacillin) or second-generation and third-generation (non-pseudomonal) cephalosporins, often achieve sub-maximal bacterial clearing with 60–70% time above the minimal inhibitory concentration ($T_{>MIC}$) and may benefit from combination therapy, while high-potency carbapenems will generate a $T_{>MIC}$ of 100% and yield no incremental benefit with the addition of a second antibiotic [33,34]. As shown by the current study, polymicrobial BSIs are usually associated with high microbial resistance pathogens and high mortality; thus, in theory, the use of combination therapy with favourable pharmacokinetic/pharmacodynamics would lead to superior survival to mono-antibiotic therapy. Further study is clearly needed to address the optimal combination therapy in patients with polymicrobial sepsis.

A recent ICU study by Sancho et al. did not find that patients with polymicrobial BSIs were associated with increased mortality as compared with patients with monomicrobial BSI [13]. High-risk microorganisms were identified as the strongest predictor of short-term mortality. It is believed that their multivariate logistic regression model suffered from co-linearity problems, as polymicrobial BSIs are highly correlated with high-risk microorganisms. The advanced PS-based IPTW weighting method was used to evaluate the survival impact of polymicrobial BSI. However, IPTW weighting has several advantages over a logistic regression model. First, the traditional logistic regression model may fail when the number of confounders is relatively large compared with the outcome events, as in this case, while PS can collapse all confounders into a summary score that can avoid the dimensionality problems associated with a large number of covariates. Second, covariate adjustment using PS in the traditional regression model results in a biased estimation of both marginal and conditional risk, while IPTW using PS allows for estimation of marginal risk with minimal bias. Lastly, an effect estimate derived from an IPTW weighting model can be interpreted as the average effect at the population level, while that of a logistic regression model can only be interpreted within the restricted population defined by the strata of covariates [21,22]. Strengths of this study include the study size, with 1166 laboratory confirmed BSI patients with a 90-day follow-up, prospective data collection, and use of advanced methodologies to minimise the effects of confounding. The prediction model was validated using a 10-fold cross validation, but the identified clinical predictors need further external validation prior to use in clinical prac-

tice. However, the results of this study should also be interpreted in light of several limitations. First, this study was performed in an Asian population, which may limit the generalisability to other non-Asian populations. It has been shown that Asian people have a higher incidence of biliary tract infection and liver abscess as compared with Caucasian or African populations [35]. Second, because of the observational nature of the study there is always a possibility for unmeasured confounding factors. Third, of the 159 patients with pneumonia, 24 (15.1%) were aspiration pneumonia and eight (5.0%) were nosocomial pneumonia. The small number of these two groups of patients prevented a meaningful comparison. In addition, recent studies have not supported a clear differentiation between aspiration pneumonia and non-aspiration pneumonia. The finding of a respiratory tract microbiome that extends from the nasal passages to the alveoli suggests that microaspiration is common, even in patients with intact mechanisms that protect the lower airways [39]. Last, although anaerobes and fungus are commonly isolated in patients with polymicrobial BSI, universal coverage of the anaerobes and fungus in the initial antibiotic regimen may lead to an overuse of antibiotics. Further investigation of risk factors for anaerobic or fungal infection among patients with polymicrobial BSI is warranted.

Conclusion

In conclusion, polymicrobial BSIs may account for 10% of all ED BSI patients. The identified clinical predictors can help early identification of suspected cases with polymicrobial infection. Polymicrobial BSIs are usually associated with high-risk Gram-negative *Enterococcus* spp., anaerobe, and *Candida* spp. infection. Knowledge of the bacteriology can guide the empiric antibiotics. Polymicrobial BSI is independently associated with higher mortality as compared with monomicrobial BSI. Use of combination antibiotics with consideration of pharmacokinetic/pharmacodynamics to cover suspected cases is a reasonable strategy to improve the outcome of this specific group of patients.

Acknowledgments

We thank the staff of the Core Labs at the Department of Medical Research in National Taiwan University Hospital for technical support, and Medical Wisdom Consulting Group for technical assistance in statistical analysis.

Declarations

Funding: This work was supported by Taiwan Ministry of Science and Technology Grants, MOST-104-2314-B-002-039-MY3 and MOST 107-2314-B-002-196, the research grant of National Taiwan University Hospital Yunlin Branch, NTUHYL108. S006, and the research grant of Far Eastern Memorial Hospital, FEMH-2019-C-038. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Competing Interests: None declared.

Ethical Approval: Not required.

Author contributions: Concept and design: Chien-Chang Lee; drafting of the manuscript: Chien-Chang Lee, Chia-Hung Yo, Yenh-Chen Hsein; revision of the manuscript for important intellectual content: Chia-Hung Yo, Yi-Luen Wu, Wan-Ting Hsu, Matthew Hui-Ming Ma, Cheng-Hsien Tsai, Shyr-Chyr Chen; statistical analysis: Chien-Chang Lee, Wan-Ting Hsu; obtaining funding: Chien-Chang Lee; supervision: Chien-Chang Lee.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.09.015.

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