Risk Factors and Outcome of Polymicrobial Bacteremia: A Retrospective Cohort Study

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ABSTRACT **Background:** Recent data regarding polymicrobial bacteremia (PMB) are lacking.

Objectives: To characterize risk factors as well as clinical, microbiological, and prognostic patterns of patients with PMB in a modern hospital setting.

Methods: A single center retrospective study including all patients diagnosed with PMB during 2013 was conducted. PMB was defined as two or more organisms cultured from the blood of the same patient within 72 hours. Patients with monomicrobial infections served as controls.

Results: There were 135 episodes (2% of all bacteremia episodes) of true PMB among 123 patients during the study period. Recent invasive procedures (odds ratio [OR] 3.59, 95% confidence interval [95%CI] 1.41–9.12, P = 0.006) and foreign bodies (OR 1.88, 95%CI 1.06–3.33, P = 0.04) were risk factors for PMB when compared with 79 patients with monomicrobial bacteremia. Central-line-associated infections were the most common infection source among patients with PMB (n=34, 28%). Enterobacteriaceae were the most commonly implicated pathogen (n=95, 77%). Non-fermenting Gram-negative bacilli were significantly more common than previously reported (n=55, 45%). Although crude 30-day mortality was higher (48% vs. 33%) in PMB patients, adjusted mortality was comparable in the two groups.

Conclusions: PMB rate in our cohort was considerably lower than in previous reports. Central-line-associated infections were more common than classic PMB sources. Mortality remained high. Strategies for early identification and better care for these patients should be pursued.

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KEY WORDS: central line infection, polymicrobial bacteremia (PMB)

Polymicrobial bacteremia (PMB) is a common clinical entity, accounting for 6–13% of positive blood cultures [1-4]. PMB is more common in patients after invasive procedures and it has been associated with immunosuppression, malignancies, and chemotherapy [1,2]. Common causes include pneumonia, as well as intra-abdominal, soft tissue, and central venous catheter infections [1-3,5,6]. The origin of approximately 25% of PMBs remain unidentified [1,7].

Several studies have found PMB to be associated with high mortality rates; roughly twice than that of monomicrobial infections [1,2,4,8,9]. In contrast, other studies showed similar mortality rates [6,10-12]. Higher mortality rates were reported in nosocomial compared with community-acquired PMB [13]. Higher mortality was also associated with inappropriate antibiotic therapy [6,14], absence of fever [9,13], and a variety of microbiological and clinical factors, the strongest associations being underlying co-morbidities and respiratory failure [1,7,15].

Most of the data on PMB were published more than 20 years ago. Current prevalence, risk factors and clinical, microbiological, and prognostic patterns of PMB are unknown. We conducted a retrospective study to address these clinically relevant issues.

PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

This retrospective cohort study was conducted at Rabin Medical Center (Beilinson Campus) in Israel. The medical center is a tertiary care, university-affiliated center. The study was approved by the hospital's institutional review board. Patients were identified through a computerized search of all positive blood cultures from January through December 2013. Patients older than 18 years of age who had at least two different microorganisms at blood cultures taken within a 72-hour period were included in the study cohort. Every patient's electronic medical file was reviewed by at least two physicians (S.G., O.I., D.S.). Collected data included demographics, functional status, immunosuppression, patient co-morbidities measured by the modified Charlson Comorbidity Index [16], and clinical data including recent surgery or invasive procedures, foreign bodies, vital signs at presentation, and laboratory results. Collected microbiological data included date of culture, microorganisms, number of bottles taken and number of positive bottles, antibiotic therapy, and infection source. Three-day, 30-day, and 1-year mortality rates were calculated for all patients starting from the PMB episode. Patient vital status was ascertained through Israel's ministry of interior database.

DEFINITIONS

PMB was defined as two or more organisms cultured from the blood of the same patient during 72 hours. Coagulase negative staphylococci, Streptococcus viridans, Bacillus spp., Micrococcus, and Corynebacteria were considered contaminants unless they grew in two or more bottles drawn on two separate occasions. A complete list of common commensals is available at http://www.cdc.gov/nhsn/XLS/master-organism-Com-Commensals-Lists.xlsx.

Patients with two or more organisms on blood cultures, with one of them representing true bacteremia and the rest defined as contaminations, were defined as monomicrobial infections. Patients with isolations of two or more organisms defined as contaminants and no true bacteremia were defined as pure contamination. Patients with a single positive blood culture of an organism considered a contaminant, without concomitant negative blood cultures, were considered to have equivocal infection. Patients with pure contamination and equivocal infection were not included in the analysis due to lack of certainty regarding true infection type. Patients with monomicrobial infections were used as a control group for risk factors, infection characteristics, and prognosis. When a patient had more than one episode of bacteremia during study period, only the first episode was included in the analysis.

All organisms were divided into seven groups, namely enterobacteriaceae, non-fermenting Gram-negative bacilli, other Gram-negative bacteria, Enterococci, Gram-positive cocci other than Enterococci, anaerobes, and Candida spp. A patient with isolation of two or more pathogens from the same group (e.g., *Escherichia coli* and *Klebsiella pneumonia*) were counted only once for the purpose of analysis of pathogen isolation patterns according to infection types.

Infections were classified according to definitions from the U.S. Centers for Disease Control and Prevention and the National Healthcare Safety Network (CDC/NHSN) surveillance [17]. Central-line-associated bacteremia was defined as bacteremia in the presence of a central line and no evidence of other sites of infection. Patients without an apparent etiology for bacteremia during hospitalization were defined as having bacteremia of unknown origin. Septic shock and sepsis were defined according to standard definitions [18]. The adequacy of empiric antimicrobial therapy was determined according to the final identification and susceptibility results of all pathogens.

Patients performance status was defined as independent vs. requiring assistance in activities of daily living. Immunosuppression was defined as active hematologic malignancy, neutropenia (< 1500/µl), s/p splenectomy, human immunodeficiency viruses, and chronic immunosuppressive treatment. Chronic corticosteroid use was considered immunosuppression at 10 mg per day of prednisone or equivalent for ≥ 3 month preceding bacteremia. Foreign bodies included central lines, pacemakers, blood vessel grafts, bone and joint implants, heart valves, common bile duct stents, urethral stents, permanent urinary catheters, and central nervous system shunts. A recent invasive procedure was defined as any procedure or surgery during 30 days prior to bacteremia.

STATISTICAL ANALYSIS

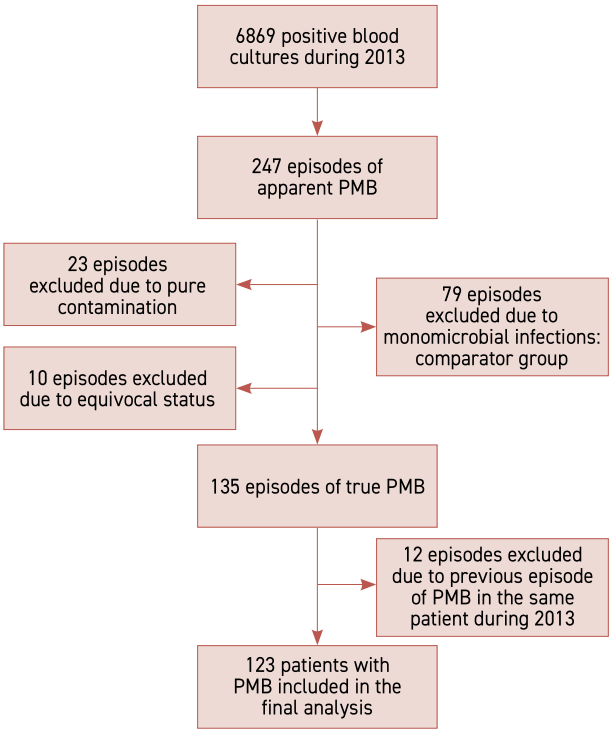
Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous variables were presented by mean ± standard deviation. Categorical variables were presented by (N, %). The *t*-test was used to compare the value of continuous variables between study groups. Chi-square (for more than two groups) or Fisher's exact test (for two groups) were used to compare the value of categorical variables among study groups. Logistic regression was used to assess the effect of variables on dichotomous endpoints (3-day, 30-day and 1-year survival). Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

During 2013, 6869 positive blood cultures were drawn in our medical center. There were 247 (3.6%) episodes of apparent PMB during this period [Figure 1]. Of the total number of episodes, 112 (1.6%) were excluded from the study cohort, 23 due to pure contamination status, 79 due to monomicrobial

Figure 1. Flow diagram for patient selection



infections with contamination, and 10 due to equivocal status. From the remaining 135 (2%) episodes of true PMB, 12 were excluded due to a previous episode of PMB in the same patient during 2013. The final study cohort included 123 patients with true PMB. The 79 patients with monomicrobial infections comprised the comparator group. Patient characteristics according to bacteremia type are detailed in Table 1. Most patients were hospitalized in general medical wards (71% of PMB and 75% of monomicrobial bacteremia). Patients with PMB had a higher median Charlson Comorbidity Index score (4 vs. 3, odds ratio [OR] 1.14, 95% confidence interval [95%CI] 1.01–1.29, $P = 0.04$). There were no significant differences in the groups according to demographics. Recent invasive procedures and foreign bodies were risk factors for PMB vs. monomicrobial infection (OR 3.59, 95%CI 1.41–9.12, $P = 0.006$, and OR 1.88, 95%CI 1.06–3.33, $P = 0.04$, respectively).

Table 1. Baseline characteristics and outcome of patients according to infection type

Patient characteristics	Polymicrobial infection (n=123)	Monomicrobial infection (n=79)	*P* value
Age (years), median (IQR)	68 (60-79)	70 (57–80)	0.86
Male sex	73 (59%)	45 (57%)	0.77
Charlson Comorbidity Index score, median (range)	4 (0–11)	3 (0–9)	0.04
Immunosuppression	25 (20.3%)	17 (21.5%)	0.86
Independence in activities of daily living	47 (42%)	32 (42%)	1
Ward			
Medical	88 (71%)	59 (75%)	0.75
Surgical	23 (19%)	9 (11%)	0.24
Intensive care	12 (10%)	11 (14%)	0.37
Foreign bodies	69 (56%)	32 (40%)	0.04
Recent invasive procedure	28 (23%)	6 (8%)	0.006
Site of infection			
Pneumonia	11 (9%)	9 (11%)	0.63
UTI	15 (12%)	20 (25 %)	0.02
Intra-abdominal infection	28 (23%)	10 (13%)	0.1
Soft tissue infection	14 (11%)	14 (18%)	0.22
Line associated infection	34 (28%)	14 (18%)	0.13
Endovascular infection	4 (3%)	4 (5%)	0.71
CNS infection	2 (2%)	1 (1%)	1
Unknown	15 (12%)	7 (9%)	0.5
All drawn blood cultures positive for bacteremia	65 (53%)	13 (16%)	< 0.001
Timing of adequate antibiotics coverage			
0 hours (empiric)	55 (45%)	38 (48%)	0.67
0–48 hours	31 (25%)	24 (30%)	0.42
> 48 hours	16 (13%)	11 (14%)	0.84
Without adequate antibiotics*	21 (17%)	6 (8%)	0.06
Septic shock	39 (32%)	21 (27%)	0.53
3-day mortality	20 (16%)	5 (6%)	0.05
30-day mortality	59 (48%)	26 (33%)	0.04
1-year mortality	70 (64%)	46 (58%)	0.46

*Without adequat antibiotics = inadequate antibiotic treatment according to microbiological sensitivity
CNS = central nervous system, IQR = interquartile range, UTI= urinary tract infection

SITE OF INFECTION

Among all cases of PMB, the most common identified infection source was central-line-associated infections (n=34, 28%), followed by intra-abdominal infections (n=28, 23%). Other causes were urinary tract infection (UTI), soft tissue infections, and pneumonia [Table 1]. Fifteen patients (12%) with PMB had an unknown infection source. Infection source diagnoses differed according to infection type, with central-line-associated infections and intra-abdominal infections accounting for most cases of PMB, while the most common etiology for monomicrobial bacteremia was UTI. These differences did not meet the pre-defined threshold for statistical significance, perhaps due to the small numbers of patients in each subgroup.

MICROBIOLOGIC DATA

Microorganisms isolated from patients with PMB according to site of infection are depicted in Table 2. Enterobacteriaceae were the most commonly implicated pathogen (n=95, 77%) followed by non-fermenting Gram-negative bacilli (n=55, 45%). Enterobacteriaceae were more common in patients with intra-abdominal infections and central-line-associated infections. Non-fermenting Gram-negative bacteria and Candida spp. were cultured mostly from patients with central-line-associated infections. Gram-positive cocci were commonly identified in patients with central-line-associated infections and soft tissue infections. The number of patients in each group was too small for statistical analysis.

Patients with PMB were more likely to have all drawn blood cultures positive for bacteremia (53% vs. 16% for polymicrobial and monomicrobial, $P < 0.001$).

Empiric antimicrobial therapy was considered adequate to treat all pathogens of PMB in 45% of patients, vs. 48% of monomicrobial infections ($P = 0.67$). More patients with PMB had not received adequate antimicrobial therapy according to microbiological sensitivity during hospitalization (17% vs. 8%, $P = 0.06$), although the difference had not reached the pre-specified threshold for statistical significance.

OUTCOME

Thirty-day mortality for PMB was significantly higher compared to monomicrobial bacteremia (48% vs. 33%, OR 1.88, 95%CI 1.04–3.38, $P = 0.04$). However, mortality rates were comparable after adjusting for age, sex, Charlson Comorbidity Index score, performance status, immunosuppression, and adequate empiric antibiotic therapy ($P = 0.1$).

Risk factors for 30-day mortality among patients with PMB

Table 2. Microorganisms isolated from patients with polymicrobial bacteremia according to site of infection

Site of infection (number)	Enterobacteriaceae (n=95, 77%)	Non-fermenting (n=55, 45%)	Enterococci (n=24, 20%)	Other Gram-positive cocci (n=27, 22%)	Anaerobes (n=10, 8%)	Candida (n=7, 6%)	Other Gram-negative (n=9, 7%)
Pneumonia (11)	8 (8%)	7 (13%)	1 (4%)	4 (15%)	0	0	1 (11%)
Urinary tract infection (15)	12 (13%)	5 (9%)	3 (12%)	2 (7%)	2 (20%)	0	0
Intra-abdominal infection (28)	26 (27%)	5 (9%)	8 (33%)	0	3 (30%)	1 (14%)	5 (56%)
Soft tissue infection (14)	12 (13%)	4 (7%)	2 (8%)	6 (22%)	2 (20%)	0	1 (11%)
Line associated infection (34)	20 (21%)	22 (40%)	6 (25%)	9 (33%)	0	6 (86%)	1 (11%)
Endovascular infection (4)	3 (3%)	3 (5%)	0	3 (11%)	0	0	0
CNS infection (2)	2 (2%)	2 (4%)	0	0	0	0	0
Unknown (15)	12 (13%)	7 (13%)	4 (17%)	3 (11%)	3 (30%)	0	1 (11%)

*Percents are for microorganism type
CNS = central nervous system

were low performance status (OR 2.9, 95%CI 1.32–6.33, P = 0.01), higher Charlson Comorbidity Index score (OR 1.17, 95%CI 1.01–1.36, P = 0.04), septic shock (OR 9.65, 95%CI 3.78–24.64, P < 0.0001), unknown source of infection vs. secondary infection (OR 3.51, 95%CI 1.0–11.9, P = 0.04), and not receiving adequate empiric antibiotic therapy (OR 2.35, 95%CI 1.13–4.88, P = 0.02).

Among patients with PMB, the lowest 30-day survival rates were documented for patients with pneumonia and PMB with unknown primary infectious source (30-day mortality 82% and 80%, respectively) followed by intra-abdominal infections (47%).

Three-day mortality rate for patients with PMB was 16%, as compared with 6% for patients with monomicrobial bacteremia (OR 2.87, 95%CI 1.03–8, P = 0.05). The highest rates (40%) were observed for patients with an unknown primary infectious source. The most significant risk factor for 3-day mortality among PMB was inadequate antibiotic therapy, with 3-day mortality of 8% for patients with adequate antibiotic coverage as compared with 57% to those without (OR 15.67, 95%CI 5.08–48.31, P < 0.001).

One-year mortality rates were similar for patients with PMB and monomicrobial bacteremia (64% and 58%, respectively).

DISCUSSION

During 2013 there were 123 patients with true PMB at our medical center. The most common etiology for PMB was central-line-associated infections, followed by intra-abdominal infections. Enterobacteriaceae were the most common pathogens, followed by non-fermenting Gram-negative bacteria. Short-term mortality was high.

PMB rate in this cohort was considerably lower than previously described [1-4,19,20], for example, Cooper et al. describes 6% [1]. Possible explanations might be more rigorous exclusion of contaminations compared to some of the previous studies, earlier diagnoses of acute bacterial infections, and evolution of blood culture technique, with more emphasis on sterility and avoidance of obtaining femoral vein blood culture. The low (n=23, 9%) pure contamination rate might be attributed to more appropriate patient selection for blood cultures.

Risk factors for PMB in our cohort included recent invasive procedures and foreign bodies, both previously described [2,3,21]. The Charlson Comorbidity Index score was higher in patients with PMB (P = 0.04). Older age was not associated with PMB, unlike in previous reports [1].

The most common PMB source in our cohort (n=34, 28%) were line associated infections. Traditional etiologies of PMB, such as intra-abdominal infections, soft tissue infections, and pneumonia, were less common. This previously unreported finding probably represents the rapidly expanding usage of central lines, which was the most common foreign body in our cohort, found in 37% of patients with PMB. While previous studies found a rising prevalence of line infections as a PMB etiology, absolute rates remained low at 3–8% [1-3,5,9] in the general patient population, and as high as 20% in ICU patients [12]. As most of the patients (70%) in this cohort were from general medical wards, these results, if replicated, represent a change from previously described PMB etiologies. A recent report of bloodstream infections among patients treated with total parenteral nutrition documented PMB in 15% of episodes, and a recent retrospective cohort of patients with severe burns found 41.5% of PMB episodes were catheter related, supporting our finding of a potential strong association between central lines and PMB [22, 23]. Of note, in a post hoc analysis, most (26/34, 76%) patients with line associated infections had no clinical signs of line infection on physical examination, as previously described in dialysis patients [24]. This observation might have

clinical significance as clinicians should probably consider removing a well-appearing central line for a patient with PMB and no other potential infectious source.

UTI was a relatively common etiology for PMB, accounting for 12% of events. Although UTI is not a classical PMB etiology, a recent report found it to be the most common etiology, more prevalent than intra-abdominal infections and pneumonia [4]. This finding might imply that the classical PMB etiologies reported in previous decades may not reflect the modern etiologies of PMB.

Unknown etiology for PMB was less common than previously reported [1,5], perhaps reflecting evolution and better availability of diagnostic imaging. Indeed, the high short-term mortality rate for patients with unknown primary infectious source probably reflects the unstable condition of these patients, making them unfit for proper workup and imaging. Thus, patients with unknown primary infectious source probably represent infection severity and not a different infectious etiology.

Patterns of microorganism isolation were mostly compatible with the clinical diagnoses. Enterobacteriaceae were the most common pathogens implicated in PMB, in accordance with previous reports. Other major bacterial groups were non-fermenting Gram-negative bacilli, Enterococci, other Gram-positive cocci and Candida spp, associated with clinically compatible infections. The most significant difference in microbiological data from most previous reports was the increased frequency of non-fermenting Gram-negative bacilli, previously reported to be < 5% [1,2,5]. This is in accordance with the rise in line associated infections in our cohort. A finding of all drawn blood cultures positive for bacteremia was strongly associated with PMB, probably partially reflecting continuous line-related bloodstream infections.

Short-term survival of patients with PMB was dismal in the lower range of previous reports [1-3,5,8-12,20]. This result can be partially explained by the stringent definitions used in our cohort. Several previous studies probably included some cases of contaminations and monomicrobial bacteremia in the PMB group. While prior reports have found that empiric antibiotic coverage rates in patients with PMB and those with monomicrobial bacteremia were similar [21], in our study we found that more patients with PMB never received adequate antibiotic therapy. Most of these patients had acute, severe infections causing rapid clinical deterioration and death. The alarmingly high 3-day mortality rate in these patients underline the life-saving significance of adequate antibiotic coverage for these patients.

LIMITATIONS

Our study had several limitations. Results from a large tertiary center might not be generalized to other hospitals, which might use fewer central line therapies. The retrospective nature makes it vulnerable to bias. We included all patients in a pre-determined calendar year to avoid selection bias and performed extensive and thorough chart review to ensure the accuracy of the analyzed clinical data to try and minimize bias risk. The inclusion of patients from all departments, although minimizing selection bias, makes the cohort population less homogenous, as different departments might have different patient populations with different prognoses. An additional limitation was the inability to conduct statistical analysis of microbiological data, due to multiple comparisons required and a limited number of patients. A larger sample size might have recognized additional risk factors for PMB compared with monomicrobial bacteremia. Our control group included only patients with monomicrobial bacteremia and contamination. We did not collect data on other patients with monomicrobial bacteremia, which also can create potential bias. Last, some of the excluded contaminations could have represent true infections [25].

CONCLUSIONS

PMB rate in our cohort was considerably lower than in previous reports. Major risk factors for PMB were foreign bodies and recent invasive procedures. Central-line-associated infections were more common than classic PMB sources, as reflected in rising rates of non-fermenting Gram-negative bacilli as part of PMB. Unknown infectious sources are less common than in previous decades. Mortality remains high. Adequate empiric antibiotic coverage is highly significant for short-term survival. Strategies for preventing catheter-associated infection should be pursued.

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Capsule

cDC1 and cancer

A subset of immune cells called conventional dendritic cell 1 (cDC1) has been shown to play a critical role in antitumor responses. **Hubert** and co-authors showed that human cDC1 contribute to antitumor responses through the production of type III interferon, also known as IFN-γ1. The authors analyzed primary breast tumors and publicly available transcriptomic data and pinpointed IFN-γ1 production by cDC1 as being associated with favorable patient outcomes and promoting a microenvironment with T helper 1 (TH1)-associated cytokines and chemokines. By treating breast cell tumor suspensions with a Toll-like receptor 3 agonist, they were able to induce TH1-polarized responses and IFN-γ1 production by cDC1. These findings provide insight into how cDC1 contribute to antitumor immunity and how they might be targeted for potential therapeutic strategies.

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Capsule

Transcriptional profiling and therapeutic targeting of oxidative stress in neuroinflammation

Oxidative stress is a central part of innate immune-induced neurodegeneration. However, the transcriptomic landscape of central nervous system (CNS) innate immune cells contributing to oxidative stress is unknown, and therapies to target their neurotoxic functions are not widely available. **Mendiola** et al. provided the oxidative stress innate immune cell atlas in neuroinflammatory disease and report the discovery of new druggable pathways. Transcriptional profiling of oxidative stress–producing CNS innate immune cells identified a core oxidative stress gene signature coupled to coagulation and glutathione-pathway genes shared between a microglia cluster and infiltrating macrophages. Tox-seq followed by a microglia high-throughput screen and oxidative stress gene network analysis identified the glutathione-regulating compound acivicin, with potent therapeutic effects that decrease oxidative stress and axonal damage in chronic and relapsing multiple sclerosis models. Thus, oxidative stress transcriptomics identified neurotoxic CNS innate immune populations and may enable discovery of selective neuroprotective strategies.

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