ORIGINAL ARTICLE

Pseudomonas aeruginosa bacteraemia: A five-year analysis of epidemiology, clinical profiles, and outcome in a Malaysian district hospital

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ABSTRACT

Introduction: *Pseudomonas aeruginosa* is known to be the epitome of nosocomial infections associated with high morbidity and mortality. The dearth of local pseudomonal studies has prompted us to conduct this study with the following objectives: (1) to examine the local pseudomonal bacteraemia (PB) epidemiology and clinical characteristics, (2) to compare the 30-day mortality among PB of different onsets and (3) to determine the predictors of 30-day mortality outcome.

Methods: This retrospective study was conducted in Hospital Seri Manjung, Perak, Malaysia. All cases of blood culture proven PB that occurred between 1st January 2015 and 31st December 2019 were reviewed. Subjects below 12 year old and whose index blood cultures grew more than one organism were excluded. Demographic, clinical and treatment data were collected using pre-tested data collection forms and analysed using SPSS version 20.0.

Results: Among the 59 subjects included, healthcare associated (HCA) infections were the most prevalent, next to hospital onset (HO) and community onset (CO) infections. The commonest underlying comorbidities were cardiovascular disease, diabetes mellitus, and chronic kidney disease. Respiratory tract was the most frequently implicated source amongst all, while the urinary tract was more frequently implicated as the source of infection among HCA cases. Seventeen patients were admitted to ICU, and they were predominantly from the HO group. Despite having a higher rate of adequate empirical antibiotics administered, the HO group reported the lowest 30-day survival rate. Multiple logistic regression analysis demonstrated the following were independent predictors of 30-day mortality: requiring mechanical ventilator support, requiring central venous line insertion, not requiring surgery, and receiving inappropriate definite antibiotics.

Conclusion: The incidence of community onset PB was appreciably low, as cases were predominantly HCA and HO in origin. Significant morbidities were observed among pseudomonal infections, with HO infections portending the worst prognosis. Lastly, prognostic factors for determining the mortality caused by PB depended more on the severity of sepsis than the timeliness of appropriate antibiotics.

KEYWORDS:
Pseudomonas aeruginosa bacteraemia, epidemiology, clinical outcome, district hospital

INTRODUCTION

Pseudomonas aeruginosa (P. aeruginosa) is a gram-negative opportunistic pathogen in humans. Pseudomonal bacteraemia (PB) has been recognized as a serious infection that is associated with increased morbidity and mortality. Generally, empirical anti-pseudomonal antibiotic is started before the availability of microbiological results.[1] This is vital because delays in administration of appropriate anti-pseudomonal antibiotics has been reported to be associated with higher mortality outcomes.[2]

According to the unpublished data, *P. aeruginosa* only accounted for 2.92 per cent of all blood culture confirmed bacteraemia (17 out of 582 isolates) that occurred in 2018 in our hospital. Despite the low incidence of PB, we recorded a disproportionately high usage of anti-pseudomonal antibiotics in recent years due to the fear of missing out PB. The treatment was frequently used in haemodialysis patients who were admitted for catheter-related blood stream infection and cases treated for hospital acquired infections. This raised concern as injudicious use of broad-spectrum antibiotics poses the risk of inducing multidrug resistant (MDR) organisms, especially in populations where the incidence PB is relatively low.[3]

To date, there is no retrieving data regarding the epidemiology and clinical characteristics of PB in the Malaysian district population. In this study, we examined the epidemiology and clinical characteristics of PB in Malaysia. In addition, we also compared the 30-day mortality among PB of different onsets and determined the predictors of 30-day mortality outcome.

METHODOLOGY

The study was conducted at the Hospital Seri Manjung (HSM), Perak, Malaysia with 258 000 semi-urban population. Among the services provided are acute medical services, intensive care services, surgical services (general and

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orthopaedic), paediatric services, women's services, and intensive care unit services. Additionally, HSM also serves as referral center for Hospital Changkat Melintang, which is a non-specialist district hospital in Manjung District.

Study Design and data collection

In this study, a retrospective analysis was performed to review all PB cases occurring between 1st January 2015 and 31st December 2019. Demographic data, clinical details and antibiotic treatment were obtained by trained medical abstractors from laboratory records, microbiology records, medical notes, nursing notes and pharmacy notes, as well as from the patient admission system.

We included all subjects aged 12 year old and above with a positive blood culture of *P. aeruginosa*. We excluded cases with incomplete or missing medical data. Also, index blood cultures which grew more than one organism were excluded.

Community onset (CO) bacteraemia was defined as that occurring within 48 hours of admission, whereas hospital onset (HO) bacteraemia was defined as after this period or cases readmitted within 48 hours after being discharged from the hospitals. Healthcare-associated (HCA) bacteraemia was defined as either one of the following: (i) patient had been admitted to HSM in the past 3 months, excluding those who were readmitted within 48 hours after being discharged from the hospitals, or (ii) from a nursing home, or (iii) had regular healthcare contact in the past 3 months, which was adapted from Friedman et al.[4]

Inter-hospital transfer cases were included if the index blood culture was collected in the emergency department of non-specialist district hospitals within the first 48 hours of presentation. If both cultures from referral hospitals and receiving hospitals grew *P. aeruginosa*, only the first index blood culture was included for analysis.

For each patient, a primary diagnosis of the source of *P. aeruginosa* infection was determined by other cultures obtained within 48 hours of the index incident blood culture drawn. In the advent that concurrent detection of *P. aeruginosa* in other sources was not available, the source of infection was presumed based on the clinical findings.

Biochemical data such as serum haemoglobin level, serum leucocyte level, absolute neutrophil count, serum platelet level, serum albumin level and serum creatinine level collected on the same day or on the nearest date from the index blood culture date were retrieved.

Sequential Organ Failure Assessment (SOFA) scores were calculated using the necessary laboratory and clinical data from patients' medical records on the same day as the index blood culture date. If multiple values were obtained on a given day, the most abnormal value was used. If a value was missing from the day of interest, the measurement from the nearest day was used in its place. If no values were available, the measurement was assumed to be normal. The organ dysfunction scores of each system would be added, thus providing a composite SOFA score between 0 and 24, which was adapted from Hattemer et al.[5]

Microbiological data

PB or blood stream infections (BSI) was defined by its isolation from one or more sets of blood culture bottles collected using standard sterile techniques. Index blood culture growing more than one organism was defined as mixed growth and was excluded from the study. Index blood culture was defined as the first blood culture that grew *P. aeruginosa*.

In HSM, all blood cultures were processed using BACTEC fluorescent series instrument 9120 (BMS diagnostics (M) Sdn Bhd). Organisms were identified to species level by Vitek 2 – Compact Machine (Biomerieux) (Diagnostic System (M) Sdn Bhd). Routine antibiotic susceptibility testing was performed according to CLSI (Clinical and Laboratory Standards Institute). Antibiotics tested for *P. aeruginosa* included Ceftazidime, Gentamicin, Amikacin, Cefoperazone, Meropenam, Imipenam, Piperacillin/Tazobactam, Ciprofloxacin and Cefepime.

The antibiotic susceptibility test was performed in adherence to Clinical and Laboratory Standard Institute (CLSI) guidelines. Multidrug resistance was defined as resistance to three or more of the following classes of agents: anti-pseudomonal carbapenems, anti-pseudomonal beta-lactams i.e., penicillins and cephalosporins, as well as aminoglycosides, and fluoroquinolones.

Appropriate empirical antimicrobial therapy was defined as therapy administered within 48 hours after blood culture samples were obtained and consisting of an initial empirical regimen containing at least one anti-pseudomonal antibiotic that was later proven to be active in vitro against blood isolates of *P. aeruginosa*. Empirical antimicrobial therapy that demonstrated intermediate sensitivity or resistance to *P. aeruginosa* was regarded as inappropriate antimicrobial therapy. Dosages, frequency, and route of antibiotic administration were also reviewed.

A delay of appropriate antimicrobial therapy was defined as the administration of inappropriate empirical antibiotics against the *P. aeruginosa* isolate prior to the availability of the results of antibiotic susceptibility testing, with a delay of more than 48 hours after blood culture samples were obtained.

The primary outcome measure was death during hospital stay and 30-day mortality rate after the index *P. aeruginosa* blood culture collection date. Due to the retrospective nature of the study, we did not attempt to determine whether 30-day mortality was attributable to the *P. aeruginosa* BSI. Out-of-hospital death was confirmed with National Registration Department, Malaysia if such information was not available in our hospital.

All the data were analyzed using Statistical Package for the Social Sciences (SPSS) Version 20. Demographic data and clinical profiles of study subjects were presented descriptively. Categorical variables among three different onset groups were compared using Pearson Chi-Square or Fisher's Exact test while continuous variables were compared using Kruskal-Wallis H test. Kaplan-Meier curve was used to compare the 30-day mortality rates among patients with CO, HCA, and

HO bacteraemia caused by *P. aeruginosa*. The event of interest was death cases that occurred within 30 days after the index blood culture date. Multiple logistic regression was used to identify variables independently associated with 30-day mortality. All variables associated with 30-day mortality in the univariate analysis ($p<0.25$) were included at model entry. A stepwise approach was used to identify independent predictors of 30-day mortality. Variables were retained in the final model if the p value was <0.05. The results of multiple logistic regression analysis were reported as adjusted odd ratios with 95% CIs. For all statistical comparisons, a p value < 0.05 was deemed significant.

RESULTS

Demographic and clinical characteristics

During the study period, a total of fifty-nine PB were included and analyzed as per onset category. We excluded 13 cases in which two cases were due to missing medical records, seven cases due to mixed growth from index blood culture and four cases due to age below 12 year old. HCA type was the most prevalent (n=27, 45.8%) among patients with PB, next to HO (n=22, 37.3%) and CO (n=10, 16.9%) type of infections. Medical ward admissions represented 72.9% of the cases (n=43). Majority of the patients admitted to ICU at presentation were HO cases (n=6). Only two multidrug resistant PB occurred during the study period, which belonged to HCA and HO type of infections. There was a male predominance in the populations studied which detailed 62.7%. The median age for CO infections was 56.0 year old (IQR: 47.0-66.8); whilst the median age for HCA and HO infections was 65.0 year old (IQR: 47.0-69.0) and 61.5 year old (IQR: 51.8-71.0) respectively (Table I).

The percentage of patients with pre-existing comorbidities was 98.3% (n=58). Among them, the three most prevalent pre-existing comorbids were cardiovascular disease (n=42, 71.2%), diabetes mellitus (n=31, 52.5%) and chronic kidney disease (n=22, 37.3%). There was a low proportion of patients with underlying haematological malignancy (n=3, 5.1%). Nine cases had pre-existing chronic wounds or pressure sores at presentation; eight of them were from the HCA category, while the remaining one was from CO patients. Eight patients with indwelling central venous line at presentation were limited to HCA cases only; whilst seven patients with indwelling urinary catheter were observed in both HCA (n=5) and HO (n=2) cases (Table I).

Of 25 patients who had shock during index blood culture, all occurred exclusively in HCA (n=14) and HO (n=11) cases (p=0.003). The median SOFA score during index blood culture was highest among HO cases (median 6.5, IQR: 3.0-14.0) and lowest among CO cases (median 4, IQR: 1.8-5.5). Neutropaenia only occurred in 5 cases (8.5%) during index blood culture (Table I).

The respiratory tract was the most frequent source (n=22, 37.3%), followed by urinary tract (n=14, 23.7%), central venous catheter (n=10, 16.9%), skin and soft tissue (n=7, 11.9%), gastrointestinal tract (n=4, 6.78%) and unknown (n=2, 3.4%). The urinary tract was more frequently implicated as the source of infection among HCA cases (p=0.012). We recorded 17 patients admitted to ICU and they were predominantly HO patients (n=14, p<0.001) as shown in Table I.

The median SOFA scores were as follows in descending order: 7.0, among patients with appropriate empirical antibiotic use; 6.0, among patients with inappropriate empirical antibiotic with non-delayed switching; 4.0, among patients with both inappropriate empirical antibiotic but delayed switching and not switched to appropriate antibiotic groups. However, this was not statistically significant (p=0.286).

Clinical Outcomes

The median haemoglobin among HCA and HO cases ranged between 7.70 g/dL and 8.85 g/dL, which were significantly lower compared to CO cases (p=0.012), with increased blood product transfusion events (p=0.003). It is also noteworthy that all groups had severe renal impairment at presentation with median creatinine ranged 226.0 to 363.0 µmol and approximately half (n=25, 42.4%) of them required dialysis treatment. There were 24 cases (40.7%) that required mechanical ventilator support and among these, 14 cases were HO infection. To note, eight cases (13.6%) underwent surgery. Types of surgery performed included open appendectomy, arthrotomy and washout for septic arthritis, wound debridement over diabetic foot ulcer and below knee amputation, incision and drainage of right leg abscess, above knee amputation for diabetic foot ulcer as well as exploratory laparotomy (Table I).

HCA and HO cases (n=26, 53.1%) were more likely to receive appropriate antibiotics compared to CO cases (n=3, 30.0%). Of 30 cases who did not receive appropriate antibiotics, nine cases were switched to appropriate antibiotics within 48 hours; 12 cases were switched to appropriate antibiotics after 48 hours and nine cases did not undergo modification of antibiotics. For the latter, reasons of not switching to appropriate antibiotics were: 2 cases took at-own-risk discharge prior to blood culture result, 4 cases passed away within 24 hours prior to blood culture result and 3 cases improved clinically with initial empirical antibiotics (Table II). Unexpectedly, the 30-day mortality rate was the lowest (16.7%) among patients who received delayed appropriate antibiotics in comparison to patients who received appropriate empirical s (55.2%) (Table III). Further analysis demonstrated that the former group of patients had a lower SOFA score (4.0 Vs 7.0).

The in-hospital mortality rate was highest among HO cases (n=14 out of 22, 63.6%) followed by HCA cases (n=10 out of 27, 37.0%) and CO cases (n=3 out of 10, 30.0%). The 30-day survival rates, stratified according to onset categories, are presented in the Kaplan-Meier Curve. It demonstrates 30.0%, 37.0% and 63.6% 30-day mortality rate in CO, HCA, and HO pseudomonal bacteraemia respectively. The HO pseudomonal bacteraemia group had the lowest probability of 30-day survival, (overall logrank test; p=0.063) as illustrated in Figure 1.

Table I: Comparison of clinical characteristics of *Pseudomonas aeruginosa* bacteraemia cases by onset category

Characteristics	CO (n=10)	HCA (n=27)	HO (n=22)	*p* value
Admission ward specialty, n(%)				
Medical	8 (80.0)	23 (85.2)	12 (54.6)	0.064[a]
Surgical	1 (10.0)	2 (7.4)	3 (13.6)	
Orthopaedic	0 (0.0)	1 (3.7)	1 (4.5)	
Intensive care unit	1 (10.0)	0 (0.0)	6 (27.3)	
Paediatric	0 (0.0)	1 (3.7)	0 (0.0)	
Age in years, median (IQR)	56.0 (47.0-66.8)	65.0 (47.0-69.0)	61.5 (51.8-71.0)	0.652[c]
Male gender, n(%)	5 (50.0)	18 (66.7)	14 (63.6)	0.644[b]
Had shock during index blood culture, n(%)	0 (0.0)	11 (40.7)	14 (63.6)	0.003[b]
Comorbidities, n(%)				
Cardiovascular disease	7 (70.0)	17 (63.0)	18 (81.8)	0.348[b]
Diabetes mellitus	5 (50.0)	12 (44.4)	14 (63.6)	0.402[b]
Chronic kidney disease/end stage renal disease	2 (20.0)	11 (40.7)	9 (40.9)	0.463[b]
Old stroke	1 (10.0)	2 (7.4)	5 (22.7)	0.358[a]
Respiratory disease	1 (10.0)	2 (7.4)	5 (22.7)	0.358[a]
Genitourinary disease	1 (10.0)	4 (14.8)	1 (4.5)	0.540[a]
Solid tumour	0 (0.0)	4 (14.8)	1 (4.5)	0.384[a]
Orthopaedic disease	1 (10.0)	3 (11.1)	1 (4.5)	0.703[a]
Chronic liver disease	1 (10.0)	2 (7.4)	1 (4.5)	0.822[a]
Haematological malignancy	0 (0.0)	3 (11.1)	0 (0.0)	0.280[a]
Human immunodeficiency virus	1 (10.0)	1 (3.7)	1 (4.5)	0.571[a]
Autoimmune disease	2 (20.0)	0 (0.0)	1 (4.5)	0.034[a]
Others*	3 (30.0)	6 (22.2)	3 (13.6)	0.426[a]
Chronic wound/pressure sore at presentation, n(%)	1 (10.0)	8 (29.6)	0 (0.0)	0.011[a]
Indwelling devices at presentation, n(%)				
Central venous line	0 (0.0)	8 (29.6)	0 (0.0)	0.005[a]
Urinary catheter	0 (0.0)	5 (18.5)	2 (9.1)	0.371[a]
Neutropaenia, i.e. neutrophils < $0.5x10^3/\mu L$	1 (10.0)	3 (11.1)	1 (4.5)	0.703[a]
Haemoglobin in g/dL, median (IQR)	12.25 (9.10-12.73)	7.70 (6.50-9.40)	8.85 (7.90-10.00)	0.012[c]
Creatinine in µmol/L, median (IQR)	226.0 (112.8-329.0)	363.0 (136.0-553.0)	257.5 (65.8-553.8)	0.378[c]
SOFA score on / nearest to index blood culture date, median (IQR)	4.0 (1.8-5.5)	5.0 (4.0-11.0)	6.5 (3.0-14.0)	0.204[c]
In-patient treatment, n(%)				
Blood product transfusion	2 (20.0)	20 (74.1)	17 (77.3)	0.003[b]
Haemodialysis	2 (20.0)	14 (51.9)	9 (40.9)	0.216[b]
Mechanical ventilator	2 (20.0)	8 (29.6)	14 (63.6)	0.019[b]
Surgery	1 (10.0)	2 (7.4)	5 (22.7)	0.358[a]
Appropriate empirical antibiotic use on index bacteraemia date, n(%)	3 (30.0)	15 (55.6)	11 (50.0)	0.383[b]
Switching of inappropriate empirical antibiotic, n(%)				0.332[a]
Not applicable	3 (30.0)	15 (55.6)	11 (50.0)	
Non-delayed switching	1 (10.0)	4 (14.8)	4 (18.2)	
Delayed switching	4 (40.0)	6 (22.2)	2 (9.1)	
Not switched	2 (20.0)	2 (7.4)	5 (22.7)	
Index blood culture source, n(%)				
Respiratory tract	4 (40.0)	6 (22.2)	12 (54.6)	0.065[b]
Urinary tract	2 (20.0)	11 (40.8)	1 (4.5)	0.012[b]
Central venous catheter	0 (0.0)	8 (29.6)	2 (9.1)	0.059[a]
Skin & soft tissue	2 (20.0)	2 (7.4)	3 (13.6)	0.506[a]
Gastrointestinal tract	2 (20.0)	0 (0.0)	2 (9.1)	0.052[a]
Unknown	0 (0.0)	0 (0.0)	2 (9.1)	0.290a
ICU admission, n(%)	1 (10.0)	2 (7.4)	14 (63.6)	<0.001[b]
In-hospital death, n(%)	3 (30.0)	9 (33.3)	14 (63.6)	0.064[b]
30-day mortality, n(%)	3 (30.0)	10 (37.0)	14 (63.6)	0.097[b]

CO, Community Onset; HCA, Healthcare Associated; HO, Hospital Onset; IQR, Interquartile range; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit

*Parkinson's disease, migraine, Bell Palsy, psychiatric disorder, gastritis, hypothyroidism, adrenal insufficiency, haemorrhoids

[a] Fisher's Exact test [b] Pearson Chi-square test [c] Kruskal-Wallis H test

Table II. Clinical Characteristics of Patients whose Inappropriate Empirical Antibiotics were Not Switched

No	Onset	Age In Years	Comorbids	30-Days Outcome	SOFA Score	Diagnosis
1	HCA	81	Advanced Prostate Carcinoma	Died	3	Urosepsis*
2	HO	79	Prostate Carcinoma	Died	4	Urosepsis*
3	HO	69	DM, Hypertension, Advanced CKD	Died	14	Perforated Diverticular Abscess**
4	HO	75	Hypertension, Dyslipidaemia	Died	14	Perforated Peptic Gastric Ulcer**
5	HO	63	DM, Hypertension, Hepatitis C, CKD	Died	3	Sepsis With Unknown Source**
6	CO	51	DM, Hypertension, Schizophrenia, Old PTB	Died	5	Community Acquired Pneumonia**
7	HCA	67	DM, Hypertension, Ischaemic Heart Disease, Diabetic Foot Ulcer	Survived	0	Infected Diabetic Foot Ulcer (Improved with intravenous ampicillin/sulbactam and wound debridement)
8	HO	57	DM, Hypertension, Dyslipidaemia	Survived	4	Hospital Acquired Infection (Improved with intravenous ceftazidime which showed intermediate sensitivity in vitro)
9	CO	65	Old Stroke	Survived	5	Aspiration Pneumonia (Improved clinically with intravenous amoxicillin/clavulanate)

CO, Community Onset; HO, Hospital Onset; HCA, Healthcare Associated; DM, Diabetes Mellitus; CKD, Chronic Kidney Disease; PTB, Pulmonary Tuberculosis; SOFA, Sequential Organ Failure Assessment
* Took At-Own Risk discharge
** Died before blood culture result was available

Table III: Comparison of Sequential Organ Failure Assessment (SOFA) score on / nearest to index blood culture date with regards to empirical antibiotic use and its switching vs. mortality

Empirical antibiotic use & its switching	SOFA score on / nearest to index blood culture date median (IQR)	30-day mortality rate
Inappropriate empirical antibiotic use & Non-delayed switching (n=9)	6.0 (3.0-10.0)	33.3%
Inappropriate empirical antibiotic use & Delayed switching (n=12)	4.0 (1.3-8.0)	16.7%
Inappropriate empirical antibiotic use & Not switched (n=9)*	4.0 (3.0-9.5)	66.7%
Appropriate empirical antibiotic use (n=29)	7.0 (4.0-13.0)	55.2%

*Four patients passed away within 24 hours after index blood culture; Two patients took At-Own-Risk discharge; Three patients responded to initial empirical antibiotics

Table IV: Independent predictors of 30-day mortality among *Pseudomonas aeruginosa* bacteraemia cases

	30-day mortality, n (%)		Multivariate analysis		
	No	Yes	Adj. OR	95% CI	*p* value[a]
Mechanical ventilator					
No	28 (80.0)	7 (20.0)	1.00		0.001
Yes	4 (16.7)	20 (83.3)	67.31	(5.58; 811.78)	
Central venous line					
No	20 (76.9)	6 (23.1)	1.00		0.018
Yes	12 (36.4)	21 (63.6)	17.54	(1.62; 190.20)	
Surgery					
No	26 (51.0)	25 (49.0)	182.15		0.031
Yes	6 (75.0)	2 (25.0)	1.00	(1.60; 20741.30)	
Switching of inappropriate empirical antibiotic					
Not applicable	13 (44.8)	16 (55.2)	1.00		0.012
Switched (Non-delayed & Delayed)	16 (76.2)	5 (23.8)	0.88	(0.11; 6.84)	0.900
Not switched	3 (33.3)	6 (66.7)	66.70	(3.08; 1444.46)	0.007

Adj. OR, Adjusted Odd Ratio; CI, Confidence Interval
[a] Wald test

Risk factors for 30-day mortality

Multivariate logistic regression analysis identified the following as independent predictors of 30-day mortality: requiring mechanical ventilator support (Adj. OR, 67.31;95% CI 5.58, 811.78; *p*=0.001), requiring central venous line insertion (Adj. OR, 17.54; 95% CI 1.62, 190.20; *p*=0.018), not requiring surgery (Adj. OR, 182.15; 95% CI 1.60, 20741.30; *p*=0.031) and receiving inappropriate empirical antibiotics which were not switched (Adj. OR, 66.70; 95% CI 3.08, 1444.46; *p*=0.007) (Table IV).

DISCUSSION

The findings of this study highlight the existence of several distinct clinical characteristics compared to previous works, which have only been focused on tertiary hospitals. According to the epidemiological study conducted locally in University of Malaya Medical Centre, the prevalence rate of haematological and non-haematological malignancies among the 87 PB cases reported were as high as 23% and 25% respectively.[6] On further note, the prevalence rate of solid tumours and leukaemia was reported to be 42.6% (58/136 cases) and 15% (21/136 cases) in the study conducted by Kang et al. in Seoul National University Hospital, Korea.[7]

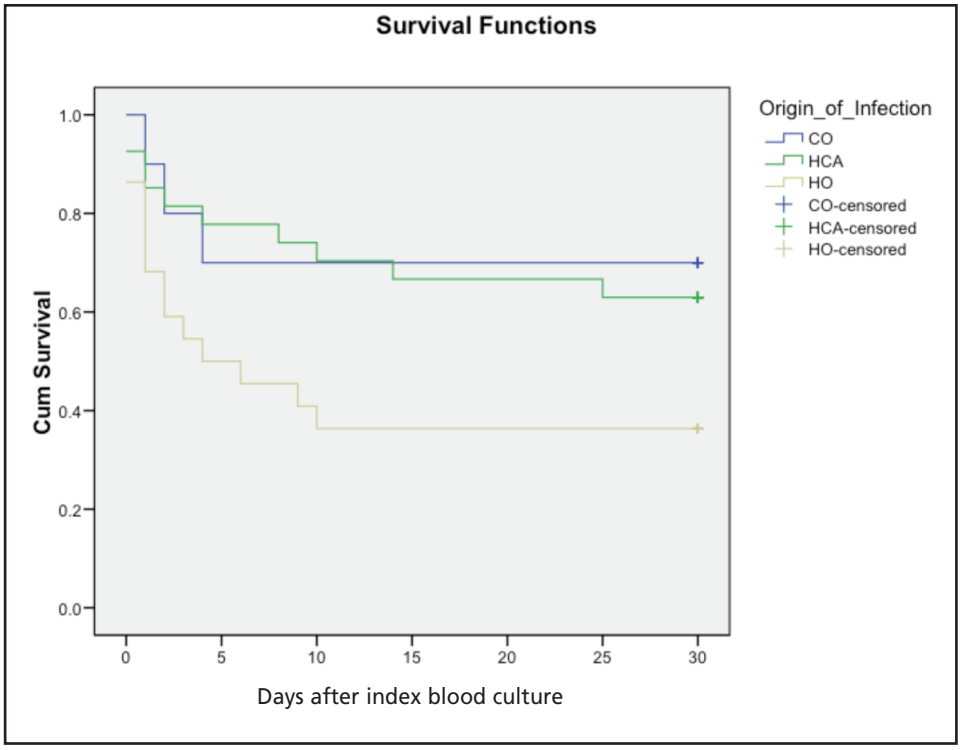

Fig. 1: Kaplan-Meier survival curve for patients with community onset VERSUS healthcare associated and hospital onset *Pseudomonas aeruginosa* bacteraemia.

In this report, we identified cardiovascular disease and diabetes mellitus as the commonest pre-existing comorbidities. The proportion of patients with underlying malignant solid tumours and haematological malignancy was considerably lower compared to available literature.[6,7] This also explains why only a minority of our cases had neutropaenia during onset of PB. These observations reflect the fact that district population clinical characteristics differ from larger hospital population characteristics in previous studies.

Apart from this slight discordance, other clinical characteristics such as male predominance and preponderance of medical admissions were similar with previous studies.[6-8] It is noteworthy that more than half of the HO cases required ICU admission. In our opinion, the actual number of pseudomonal cases requiring intensive care could be substantially higher if not for ICU bed limitations. Encouragingly, multi-drug resistant *P. aeruginosa* were appreciably low with only two cases recorded in this series. Further analysis showed that these cases had recent admission to tertiary hospitals, and this substantiates the absence of community origin MDR *P. aeruginosa* in our population.

While many studies have rigorously examined the severity of PB via sepsis scoring system, few have investigated the need of haemodialysis support and blood transfusion requirement during admission. In this study, we discovered a large number of HCA and HO pseudomonal bacteraemia requiring haemodialysis support and blood product transfusion. The detrimental impact of pseudomonal infections was also reflected from the strikingly high serum creatinine levels and profound anaemia observed during index blood culture dates. These data emphasize the importance of close monitoring of renal function and haemoglobin trend during the course of hospitalization. Also, avoidance of nephrotoxic drugs during the course of treatment is crucial as they have a predisposition to develop severe renal complications. By the same principle, our hospital antibiotic guidelines do not recommend aminoglycosides as empirical anti-pseudomonal antibiotics due to this concern.

The incidence of catheter related blood stream infections (CRBSI) among end stage renal failure (ESRF) patients are expected to be on the rising trend due to the escalating numbers of ESRF patients.[9] In this series, the incidence of pseudomonal CRBSI was considerably low with only eight HCA CRBSI in the entire five years. To date, guidelines for CRBSI treatment are largely based on empirical work done overseas.[10-13] These findings raise the question of whether *P. aeruginosa* are truly frequently accountable for CRBSI locally and the role of combination anti-pseudomonal antibiotics for all CRBSI cases. Decisions regarding whether to initiate empirical anti-pseudomonal antibiotics should reflect a balance between the risk of delayed appropriate treatment and risk of unnecessary broad spectrum antibiotic usage which promotes the emergence of MDR organisms Therefore, we recommend future studies to examine the epidemiology of CRBSI locally to identify the risk factors that predispose towards pseudomonal CRBSI that would enable restriction of usage of combination anti-pseudomonal antibiotics to the at-risk groups only.

It is well-proven and established that delayed administration of appropriate antibiotics was associated with increased mortality outcomes. This had been proven by Cheo-In et al who found increased mortality among PB cases who received delayed effective antimicrobial antibiotics which is defined as more than 24 hours after blood culture samples were taken.[2] Interestingly, our results do not appear to corroborate with their observations; in fact, we found that despite higher rate of appropriate empirical antibiotic usage among cases with HCA and HO infections, they trend towards higher mortality compared to those who received delayed effective antibiotics.

There are several possible explanations for these rather contradictory observations. First and foremost, an increased SOFA score appears to be the determinant factor for higher mortality, and timely effective antibiotics did not seem to alter the course of patients with high burden of morbidity. Nevertheless, we could not find statistical evidence of this as an independent predictor of mortality. Other factors such as morbid debility, multiple comorbidities and advanced age which could similarly have a negative influence in prognosis which would not be reflected in SOFA scores should be taken into account as well.[14] It is interesting to discover that patients who underwent surgery had a better 30-day survival. Hence, we can reasonably recommend that surgery alongside anti-pseudomonal antibiotics be considered if the pseudomonal source is surgically eradicable.

The strength of this study lies in it being the first Malaysian study in a district hospital and the results provide considerable insight into PB epidemiology in the country. The limitations of this study are that it was a single-centre retrospective study, and the number of cases was small. Therefore, it is plausible that we could have underestimated the significance of certain variables. Nevertheless, measures were taken to ensure the rigor of this study, which include use of clear variable definitions and application of statistical analysis. Importantly, clinical data abstractors comprising of trained medical officers from the Internal Medicine Department at HSM mitigated the risk of data collection errors.

In conclusion, community onset PB cases remained scarce in the district hospital, with the majority of cases belonging to healthcare associated and hospital onset infections. Also, PB was fraught with high morbidity with an increased predisposition to haemodialysis, blood transfusion, mechanical ventilator support and ICU care. Lastly, the prognostic factor for mortality of PB depended more on the severity of sepsis rather than the timeliness of appropriate antibiotics.

ETHICAL APPROVAL

This study was registered with National Medical Research register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH). MREC Approval Letter: KKM/NIHSEC/P20-100 (5) dated 21st January 2020. NMRR ID: NMRR-19-3550-52195.

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