ORIGINAL ARTICLE

# Risk factors and outcome of community onset *Pseudomonas aeruginosa* bacteraemia in two Malaysian district specialist hospitals

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**ABSTRACT**

**Introduction: Despite the ever-growing number of community onset (CO) *Pseudomonas aeruginosa (P. aeruginosa)* bacteraemia, there is a dearth of district hospital-based research examining this significant infection, which is associated with high mortality. The objectives of this study were as following: (1) to determine the risk factors of CO *P. aeruginosa* bacteraemia, (2) to compare the 30-day mortality rate between *P. aeruginosa* and *Escherichia coli* bacteraemia and (3) to identify the predictors of 30-day mortality for CO gram negative bacteraemia.**

**Methods: This is a retrospective case control study in Hospital Seri Manjung and Hospital Teluk Intan, Perak, Malaysia. *P. aeruginosa* bacteraemia cases that occurred between 1st January 2015 to 31st December 2019 were included, whilst *E. coli* bacteraemia cases that occurred within the same period were recruited successively until 1:2 case control ratio was achieved. Subjects below 12-year-old and those with polymicrobial bacteraemia were excluded. Demographic, clinical and treatment data were collected using pre-tested data collection forms by trained investigators.**

**Results: A total of 61 patients with *P. aeruginosa* bacteraemia and 122 patients with *E. coli* bacteraemia were included. Recent admission in the earlier three months, regular haemodialysis, immunosuppressive therapy in the past 30 days, chronic wound/pressure sore at presentation and indwelling urinary catheter at presentation were identified as independent predictors of CO pseudomonal bacteraemia. Whilst older age was identified as a negative predictor of CO Pseudomonal bacteraemia (all $p<0.05$). The 30-day mortality rate was 34.4% in subjects with *P. aeruginosa* bacteraemia and 27.0% in those with *E. coli* bacteraemia ($p=0.302$). Predictors of 30-day mortality for community onset gram negative bacteraemia were as follow: older age, underlying solid tumours, neutropaenia at presentation, in-patient mechanical ventilation, and in-patient nasogastric tube insertion. Unexpectedly, receipt of inappropriate empirical antibiotics which was switched later (delayed and non-delayed switching) was identified as the negative predictors of mortality (all $p<0.05$).**

**Conclusion: It is prudent to restrict the usage of empirical anti-pseudomonal antibiotics among individuals at risk as liberal usage of broad-spectrum antibiotics engenders emergence of drug resistant organism, particularly in district setting where community onset pseudomonal bacteraemia remains scarce. Subjects with elevated risk of mortality should receive early escalation of care as per sepsis management guidelines.**

**KEYWORDS:**
*Risk factors, Outcome, Community onset, Pseudomonas aeruginosa bacteraemia*

## INTRODUCTION

*Pseudomonas aeruginosa*, which is a gram negative aerobic bacilli, displays a predilection for infecting immunocompromised individuals and systemic pseudomonal infections are associated with dismal outcomes, with mortality rate reported as high as 46%.[1] In recent years, community onset (CO) *P. aeruginosa* bacteraemia has been increasingly reported.[2,3] This poses great challenges to the clinicians as differentiating pseudomonal bacteraemia (PB) from non-pseudomonal bacteraemia infection are difficult due to the lack of pathognomonic signs and their inherent resistance to a wide-ranged of antibiotics.[4]

Considering the deleterious outcomes associated with delayed effective antibiotics therapy in systemic pseudomonal infection, the notion of maintaining a low threshold for the usage of anti-pseudomonal may seem to be an appealing pursuit. Yet, the harms of injudicious usage of anti-pseudomonal antibiotics are also equally notable. The unguided and rampant use of broad-spectrum antibiotics would lead to emergence of multi-drug resistant organisms which would increase the costs of care and ultimately deplete the already very limited armamentarium we have in the present post-antibiotic era.[5] From a theoretical point of view, characterisation of pseudomonal blood stream infection would enable an educated and restrictive use of anti-pseudomonal antibiotics among the at-risk individuals.

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To our best knowledge, the literature on the risk factors of community onset *P. aeruginosa* bacteraemia is limited to studies conducted in tertiary hospitals, which has a distinct population demography compared to our district populations.[1] In view of this, we undertook this study with the following objectives (1) to determine the risk factors of CO *P. aeruginosa* bacteraemia, (2) to compare the 30-day mortality rate between *P. aeruginosa* and *Escherichia coli* bacteraemia and (3) to identify the predictors of 30-day mortality for CO gram negative bacteraemia.

## MATERIALS AND METHODOLOGY

In the capacity of being specialist district hospitals in the state of Perak, both Hospital Seri Manjung (HSM) and Hospital Teluk Intan (HTI) receive referral cases from peripheral district hospitals who require in-patient attention. HSM receives transfer cases from Hospital Changkat Melintang, Perak whereas HTI receives referrals from Hospital Tapah and Hospital Sabak Bernam, which are located in the neighbouring state of Selangor, Malaysia.

### Study Design and Data Collection

This is a retrospective 1:2 matched case-control study involving two healthcare centres, HSM and HTI. The investigators reviewed records of hospitalised patients with reported *P. aeruginosa* growth in blood culture between 1st January 2015 to 31st December 2019, whilst *E. coli* bacteraemia cases that occurred within the same period were recruited in an accumulative manner until 1:2 case control ratio was achieved. *E. coli* bacteraemia was selected as the controls because these were the most reported Gram-negative organism in both centres. Data from these patients were cross-checked with admission data and were included if positive cultures occurred within 48 hours after hospitalisation.

Their clinical data during the admission were obtained via electronic or physical copies. Demographic data including age, gender and residential status were recorded. Clinical characteristics including previous admissions, fever, use of vasoactive drug therapy, pre-existing comorbidities, use of immunosuppressive therapy, presence of indwelling devices, biochemical indices on admission, blood transfusions, mechanical ventilation, invasive procedures performed, antibiotic usage, antibiotic susceptibility for index blood culture, and clinical outcome were recorded. Investigators also recorded changes in antibiotics during the duration of hospitalisation, whether or not it was done before 48 hours, between 48 hours to 5 days, or after 5 days of admission. Data from previous admissions occurring within the last 3 months were also reviewed for past infection, antibiotic use, previous procedures, or long-term healthcare exposure for wound dressing, catheter change, or haemodialysis.

All subjects aged 12-year-old and above with a positive growth of either *P. aeruginosa* or *E. coli* on the index blood culture upon admission within the first 48 hours were included. Cases with incomplete clinical data or polymicrobial bacteraemia were excluded. Demographic, clinical and treatment data were collected using pre-tested data collection forms by trained investigators.

CO bacteraemia was defined as positive bacteria growth detected within 48 hours of hospital admission. Cases which were readmitted within 48 hours after being discharged from the hospitals would be considered as hospital onset bacteraemia and hence would not be included in this study. Previous admission was defined as admission that occurred within the last three months prior to the index admission.

The presence of *P. aeruginosa* bacteraemia or *E. coli* bacteraemia was defined by the identification from one or more sets of blood culture bottles collected using standard sterile techniques. Index blood culture was defined as the first blood culture that grew *P. aeruginosa* or *E. coli*. Index blood cultures also included patients who were transferred from peripheral district hospitals whose cultures were obtained within the first 48 hours of presentation to their respective hospitals.

Sequential Organ Failure Assessment (SOFA) scores were tabulated based on available laboratory and clinical data from patients' medical records on the same day as index blood culture date. In the event multiple blood samples or clinical assessments were made, investigators recorded the most abnormal value available from the said date. When specific parameters required in measuring SOFA scores were unavailable on the date of index blood culture, investigators used the parameters nearest to the date in measuring SOFA scores. A primary diagnosis of the source of *P. aeruginosa* or *E. coli* was obtained based on clinical findings, radiological data or other cultures obtained within 48 hours of the index incident blood culture drawn.

### Microbiological Data

In both centres, blood cultures were processed using BACTEC fluorescent series instrument 9120 and 9240 (BMS diagnostics (M) Sdn. Bhd.). Organisms were identified to species level by Vivek 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, Meropenem, Imipenem, Piperacillin/Tazobactam, Ciprofloxacin and Cefepime. Antibiotics tested for *E.coli* included Ceftazidime, Cefotaxine, Ciprofloxacin, Gentamicin, Imipenem, Meropenem, Ampicillin, Amoxicillin/Clavulunate, Amikacin, Ampicillin/Sulbactam, Piperacillin/Tazobactam, Cefuroxime, Cotrimoxazole and Ceftriaxone. Non-susceptible include antibiotics that are reported as 'intermediate' and 'resistance' in susceptibility testing results. Multidrug resistance is defined as resistance to more than three of the following agents: anti-pseudomonal carbapanems, anti-pseudomonal beta-lactams (penicillins and cephalosporins), aminoglycosides, and fluroquinolones.

We considered empirical antimicrobial therapy as appropriate when: a) administered within 48 hours after index blood culture samples, and b) the regimen contains at least one antibiotic that is active against blood isolates in vitro. The dosage, frequency and route of antibiotics administered were reviewed. Delay in appropriate antimicrobial therapy referred to an initial inappropriate empirical antibiotics against isolate, which was later switched to an appropriate antibiotic after a lapse of more

than 48 hours from the time which blood culture samples were obtained.

All the data were analysed using Statistical Package for the Social Sciences (SPSS) Version 20. Demographic data and clinical profiles of study subjects were presented descriptively. Categorical variables between cases and controls were compared using Pearson Chi-Square or Fisher's Exact test while continuous variables were compared using Student t test or Mann-Whitney U test. Kaplan-Meier curve was used to compare the 30-day mortality rates among patients with *P.aeruginosa* bacteraemia and *E.coli* bacteraemia. 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 *P. aeruginosa* bacteraemia and variables independently associated with 30-day mortality among all the subjects studied. All variables associated with *P. aeruginosa* bacteraemia and 30-day mortality in the univariate analysis ($p<0.25$) were included at model entry. A stepwise approach was used to identify independent risk factors of *P. aeruginosa* bacteraemia and 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% Confidence Intervals (95%CI). For all statistical comparisons, a $p$-value <0.05 was deemed significant.

## RESULTS

### Study populations and clinical characteristics

A total of 61 patients with blood culture proven *P. aeruginosa* bacteraemia were identified and included in the analysis as case group. The cases were matched with 122 patients with blood culture confirmed *E. coli* bacteraemia during the study period to generate a 1:2 ratio between case subjects and control subjects (Table I). Among the 18 cases that were excluded, 10 cases were mixed growth, four cases were below 12-year-old and four cases due to missing clinical notes.

A review of the baseline characteristics revealed that gender distribution was relatively equal in the case subjects as opposed to the control subjects which were predominantly females (50.8% vs. 70.5%; $p=0.009$). Also, case subjects are generally younger compared to the control subjects (mean age in years 59.2 vs. 64.5; $p=0.019$). The commonest comorbidities among pseudomonal group were cardiovascular disease (36 cases), diabetes mellitus (DM) (28 cases) and chronic kidney disease or end stage renal disease (26 cases). The prevalence of chronic kidney disease or end stage renal failure (42.6% vs. 10.7%; $p<0.001$), haematological malignancy (8.2% vs 0.0%; $p=0.004$) and autoimmune disease (4.9% vs. 0.0%; $p=0.036$) in case groups were significantly higher compared to control groups. Noticeably, haematological malignancy, autoimmune disease and human immunodeficiency virus infection were only present in the case cohort but at a very small number. In contrast, DM (66.4% vs. 45.9%; $p=0.008$) was more prevalent among control group compared to case group (Table I).

The percentage of recent immunosuppressive treatment (11.5% vs. 0.8%; $p=0.002$) and presence of pre-existing chronic wound or pressure sore (19.7% vs. 4.9%, $p=0.002$) were higher among pseudomonal group. Furthermore, indwelling central venous line (23.0% vs. 0.8%, $p<0.001$), urinary catheter (11.5% vs 2.5%; $p=0.017$) and Tenckhoff catheter (3.3% vs. 0.0%; $p=0.110$) were also more frequently observed among pseudomonal group (Table I).

There was a significant difference between case subjects and control subject in terms of regular healthcare exposure (44.3% vs. 6.6%; $p<0.001$) and recent admission (52.5% vs. 14.8%; $p<0.001$) during the last three months prior to index admission. Further analysis revealed that types of healthcare exposure were due to long term haemodialysis (16 cases), wound dressing (5 cases), urinary catheter exchange (4 cases) and Ryle's tube exchange (2 cases) as shown in Table I.

On the other hand, past admission treatment review indicated a higher exposure rate to penicillin (18.0% vs 4.1%; $p=0.002$) and cephalosporin (24.6% vs. 5.7%; $p<0.001$) among pseudomonal group. In this report, multi-drug resistant organisms exclusively occurred in the control subjects which recorded 22 cases of extended spectrum beta-lactamase producing *E. coli* ($p<0.001$) despite lower exposure rate to penicillin and cephalosporin. Notably, central venous line insertion (14.8% vs. 2.5%; $p=0.003$), haemodialysis (16.4% vs. 1.6%; $p<0.001$), blood products transfusion (18.0% vs. 5.7%; $p=0.008$) and surgery (9.8% vs. 0.0%; $p=0.001$) were more often performed on the case subjects during the recent admission (Table I).

### Clinical Outcomes

Pseudomonal subjects were more ill during presentation as evidenced by the higher median SOFA score (5.0 vs. 3.0; $p=0.002$). They also demonstrated higher rate of shock during first 48 hours of presentation (32.8% vs. 26.2%; $p=0.354$) although this was not statistically significant. Interestingly, the proportion of intensive care unit (ICU) admission were higher among *E. coli* group (9.8% vs. 4.9%; $p=0.253$) although this was not statistically significant (Table I).

Evaluation of biochemical parameters showed that median haemoglobin (8.95g/dL vs. 11.71g/dL; $p<0.001$) and mean albumin level (24.0g/dL vs. 27.1g/dL; $p=0.010$) were remarkably lower in the pseudomonal group. On the other hand, the serum creatinine (303.0µmol/L vs. 154.5µmol/L; $p<0.001$) levels were significantly higher in the pseudomonal group. Neutropaenia only occurred in pseudomonal group (8.2% vs. 0.0%; $p=0.004$). Examination of the bacteraemia sources identified central venous catheter infections (23.0% vs. 0.0%; $p<0.001$), and skin and soft tissue infections (11.5% vs. 1.6%; $p=0.007$) more frequent implicated in the pseudomonal group, whereas urinary tract infections (41.8% vs 24.6%; $p=0.022$), gastrointestinal tract infections (16.4% vs. 4.9%; $p=0.027$) and hepatobiliary tract infections (4.1% vs. 0.0%; $p=0.171$) were more common among the *E. coli* group. Presence of concomitant bacteria growth were conspicuously lower in the *E. coli* cohort (13.1% vs. 32.8%; $p=0.002$) as depicted in Table I.

**Table I: Comparison of clinical characteristics of community onset bacteraemia (*P. aeruginosa* Vs. *E. coli*)**

| Characteristics | *P.aeruginosa* (n=61) | *E.coli* (n=122) | *p* value |
|---|---|---|---|
| **Admission ward specialty, n(%)** | | | 0.582[a] |
| Medical | 54 (88.5) | 113 (92.6) | |
| Non-medical | 6 (9.9) | 7 (5.8) | |
| ICU | 1 (1.6) | 2 (1.6) | |
| **Multidrug-resistant organism, n(%)** | 0 (0.0) | 22 (18.0) | <0.001[b] |
| **Age in years, mean (SD)** | 59.2 (15.5) | 64.5 (13.6) | 0.019[c] |
| **Male gender, n(%)** | 30 (49.2) | 36 (29.5) | 0.009[b] |
| **Admitted in the past 3 months, n(%)** | 32 (52.5) | 18 (14.8) | <0.001[b] |
| **Previous admission: Antibiotic use, n(%)** | | | |
| Cephalosporin | 15 (24.6) | 7 (5.7) | <0.001[b] |
| Penicillin | 11 (18.0) | 5 (4.1) | 0.002[b] |
| Nitroimidazole | 3 (4.9) | 2 (1.6) | 0.335[a] |
| Macrolide | 1 (1.6) | 2 (1.6) | 1.000[a] |
| Carbapenem | 2 (3.3) | 0 (0.0) | 0.110[a] |
| **Previous admission: In-patient treatment, n(%)** | | | |
| Urinary catheter | 13 (21.3) | 13 (10.7) | 0.052[b] |
| Blood product transfusion | 11 (18.0) | 7 (5.7) | 0.008[b] |
| Haemodialysis | 10 (16.4) | 2 (1.6) | <0.001[a] |
| Central venous line | 9 (14.8) | 3 (2.5) | 0.003[a] |
| Nasogastric tube | 4 (6.6) | 5 (4.1) | 0.484[a] |
| Surgery | 6 (9.8) | 0 (0.0) | 0.001[a] |
| Endoscopy | 3 (4.9) | 2 (1.6) | 0.335[a] |
| **Regular healthcare exposure in the last 3 months, n(%)** | 27 (44.3) | 8 (6.6) | <0.001[b] |
| **Types of regular healthcare exposure in the last 3 months, n(%)** | | | |
| Haemodialysis | 16 (26.2) | 1 (0.8) | <0.001[b] |
| Wound dressing | 5 (8.2) | 2 (1.6) | 0.042[a] |
| Urinary catheter change | 4 (6.6) | 2 (1.6) | 0.096[a] |
| Ryle's tube change | 2 (3.3) | 3 (2.5) | 1.000[a] |
| **Had shock during index blood culture, n(%)** | 20 (32.8) | 32 (26.2) | 0.354[b] |
| **Comorbidities, n(%)** | | | |
| Cardiovascular disease | 36 (59.0) | 81 (66.4) | 0.327[b] |
| Diabetes mellitus | 28 (45.9) | 81 (66.4) | 0.008[b] |
| Chronic kidney disease/end stage renal disease | 26 (42.6) | 13 (10.7) | <0.001[b] |
| Old stroke | 4 (6.6) | 15 (12.3) | 0.230[b] |
| Respiratory disease | 6 (9.8) | 10 (8.2) | 0.711[b] |
| Solid tumour | 6 (9.8) | 9 (7.4) | 0.568[b] |
| Genitourinary disease | 4 (6.6) | 7 (5.7) | 1.000[a] |
| Chronic liver disease | 4 (6.6) | 4 (3.3) | 0.444[a] |
| Orthopaedic disease | 3 (4.9) | 4 (3.3) | 0.688[a] |
| Haematological malignancy | 5 (8.2) | 0 (0.0) | 0.004[a] |
| Autoimmune disease | 3 (4.9) | 0 (0.0) | 0.036[a] |
| Human immunodeficiency virus | 2 (3.3) | 0 (0.0) | 0.110[a] |
| Others* | 13 (21.3) | 14 (11.5) | 0.077[b] |
| **Immunosuppressive therapy in the past 30 days, n(%)** | 7 (11.5) | 1 (0.8) | 0.002[a] |
| **Chronic wound/pressure sore at presentation, n(%)** | 12 (19.7) | 6 (4.9) | 0.002[b] |
| **Indwelling devices at presentation, n(%)** | | | |
| Central venous line | 14 (23.0) | 1 (0.8) | <0.001[b] |
| Urinary catheter | 7 (11.5) | 3 (2.5) | 0.017[a] |
| Tenckhoff | 2 (3.3) | 0 (0.0) | 0.110[a] |
| **Laboratory findings at index blood culture date** | | | |
| Haemoglobin, g/dL, mean (SD) | 8.95 (2.63) | 11.71 (2.27) | <0.001[c] |
| White cell count, x10$^3$/µL, median (IQR) | 13.20 (14.90) | 17.20 (11.08) | 0.103[d] |
| Albumin, g/L, mean (SD) | 24.0 (7.7) | 27.1 (7.5) | 0.014[c] |
| Creatinine, µmol/L, median (IQR) | 303.0 (416.5) | 154.5 (143.0) | <0.001[d] |
| **Neutropaenia, i.e. neutrophils < 0.5x10$^3$/µL** | 5 (8.2) | 0 (0.0) | 0.004[a] |
| **SOFA score on / nearest to index blood culture date, median (IQR)** | 5.0 (5.0) | 3 (6.0) | 0.002[d] |
| **Current admission: In-patient treatment, n(%)** | | | |
| Central venous line | 28 (45.9) | 20 (16.4) | <0.001[b] |
| Blood product transfusion | 27 (44.3) | 12 (9.8) | <0.001[b] |
| Haemodialysis | 23 (37.7) | 11 (9.0) | <0.001[b] |
| Mechanical ventilator | 11 (18.0) | 20 (16.4) | 0.780[b] |
| Surgery | 5 (8.2) | 6 (4.9) | 0.510[a] |
| **Appropriate empirical antibiotic use on index bacteraemia date, n(%)** | 30 (49.2) | 95 (77.9) | <0.001[b] |

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**Table I: Comparison of clinical characteristics of community onset bacteraemia (*P. aeruginosa* Vs. *E. coli*)**

| | | | |
|---|---|---|---|
| **Switching of inappropriate empirical antibiotic, n(%)** | | | 0.001[b] |
| Not applicable | 30 (49.2) | 95 (77.9) | |
| Non-delayed switching | 5 (8.2) | 3 (2.4) | |
| Delayed switching | 14 (22.9) | 15 (12.3) | |
| Not switched | 12 (19.7) | 9 (7.4) | |
| **Index blood culture source, n(%)** | | | |
| Urinary tract | 15 (24.6) | 51 (41.8) | 0.022[b] |
| Respiratory tract | 21 (34.4) | 42 (34.5) | 1.000[b] |
| Gastrointestinal tract | 3 (4.9) | 20 (16.4) | 0.027[b] |
| Central venous catheter | 14 (23.0) | 0 (0.0) | <0.001[a] |
| Skin & soft tissue | 7 (11.5) | 2 (1.6) | 0.007[a] |
| Hepatobiliary tract | 0 (0.0) | 5 (4.1) | 0.171[a] |
| Unknown | 1 (1.6) | 2 (1.6) | 1.000[a] |
| **Other samples with concomitant bacteria growth, n(%)** | 20 (32.8) | 16 (13.1) | 0.002[b] |
| **ICU admission, n(%)** | 3 (4.9) | 12 (9.8) | 0.253[b] |
| **In-hospital death, n(%)** | 20 (32.8) | 28 (23.0) | 0.154[b] |
| **30-day mortality, n(%)** | 21 (34.4) | 33 (27.0) | 0.302[b] |

SD, Standard deviation; IQR, Interquartile range; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit
* psychiatric disorder, migraine, haemorrhoids, gastritis, hypothyroidism, Bell Palsy, cholelithiasis, pancytopenia, idiopathic thrombocytopenic purpura, epilepsy, recurrent pyogenic cholangitis with hepatolithiasis, deep vein thrombosis
[a] Fisher's Exact test
[b] Pearson Chi-square test
[c] Independent t-test
[d] Mann Whitney U test

**Table II: Comparison of SOFA score on / nearest to index blood culture date with regards to empirical antibiotic use and its switching vs. mortality**

| Empirical antibiotic & its switching | SOFA score, median (IQR) | *p* value | 30-day mortality rate | *p* value | Empirical antibiotic & its switching | SOFA score, median (IQR) | *p* value | 30-day mortality rate | *p* value |
|---|---|---|---|---|---|---|---|---|---|
| ***Pseudomonas aeruginosa* bacteraemia (n=61)** | | 0.226[a] | | 0.087[b] | ***Escherichia coli* bacteraemia (n=122)** | | 0.613[a] | | 0.093[b] |
| **Appropriate empirical antibiotic (n=30)** | 6.5 (4.3) | | 36.7% | | **Appropriate empirical antibiotic (n=95)** | 3.0 (6.0) | | 28.4% | |
| **Inappropriate empirical antibiotic & Non-delayed switching (n=5)** | 4.0 (8.5) | | 0.0% | | **Inappropriate empirical antibiotic & Non-delayed switching (n=3)** | 5.0 (5.0) | | 66.7% | |
| **Inappropriate empirical antibiotic & Delayed switching (n=14)** | 4.5 (6.5) | | 21.4% | | **Inappropriate empirical antibiotic & Delayed switching (n=15)** | 4.0 (5.0) | | 6.7% | |
| **Inappropriate empirical antibiotic & Not switched (n=12)** | 4.0 (5.3) | | 58.3% | | **Inappropriate empirical antibiotic & Not switched (n=9)** | 2.0 (4.5) | | 33.3% | |

SOFA, Sequential Organ Failure Assessment
[a] Kruskal-Wallis H test
[b] Fisher's Exact test

**Table III: Independent risk factors for community onset *Pseudomonas aeruginosa* bacteraemia**

| Variable | Multivariate analysis | | |
|---|---|---|---|
| | Adj. OR | 95% CI | *p* value[a] |
| Age | 0.97 | (0.94, 1.00) | 0.048 |
| Admitted in the past 3 months | 4.06 | (1.73, 9.53) | 0.001 |
| Regular healthcare exposure: Haemodialysis | 44.13 | (5.36, 363.27) | <0.001 |
| Immunosuppressive therapy in the past 30 days | 13.82 | (1.41, 135.43) | 0.024 |
| Chronic wound/pressure sore at presentation | 4.49 | (1.32, 15.32) | 0.016 |
| Urinary catheter at presentation | 7.17 | (1.30, 39.49) | 0.024 |

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

**Table IV: 30-day mortality predictors of community onset gram negative bacteraemia**

| Variable | 30-day mortality, n (%) | | | Multivariate analysis | |
|---|---|---|---|---|---|
| | No | Yes | Adj. OR | 95% CI | *p* value[a] |
| **Age in years, mean (SD)** | 60.3 (14.7) | 68.6 (11.9) | 1.06 | (1.02, 1.10) | 0.005 |
| **Solid tumour** | | | | | 0.004 |
| No | 121 (72.0) | 47 (28.0) | 1.00 | | |
| Yes | 8 (53.3) | 7 (46.7) | 7.80 | (1.91, 31.82) | |
| **Neutropaenia, i.e. neutrophils < 0.5x10$^3$/μL** | | | | | 0.021 |
| No | 127 (71.3) | 51 (28.7) | 1.00 | | |
| Yes | 2 (40.0) | 3 (60.0) | 23.10 | (1.62, 328.88) | |
| **In patient treatment: Mechanical ventilator** | | | | | <0.001 |
| No | 125 (82.2) | 27 (17.8) | 1.00 | | |
| Yes | 4 (12.9) | 27 (87.1) | 14.43 | (3.54, 58.80) | |
| **In patient treatment: Nasogastric tube** | | | | | <0.001 |
| No | 116 (86.6) | 18 (13.4) | 1.00 | | |
| Yes | 13 (26.5) | 36 (73.5) | 10.88 | (3.49, 33.92) | |
| **Switching of inappropriate empirical antibiotic** | | | | | 0.037 |
| Not applicable | 87 (69.6) | 38 (30.4) | 1.00 | | |
| Switched (Non-delayed & Delayed) | 31 (83.8) | 6 (16.2) | 0.20 | (0.05, 0.83) | 0.026 |
| Not switched | 11 (52.4) | 10 (47.6) | 1.74 | (0.46, 6.57) | 0.414 |

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

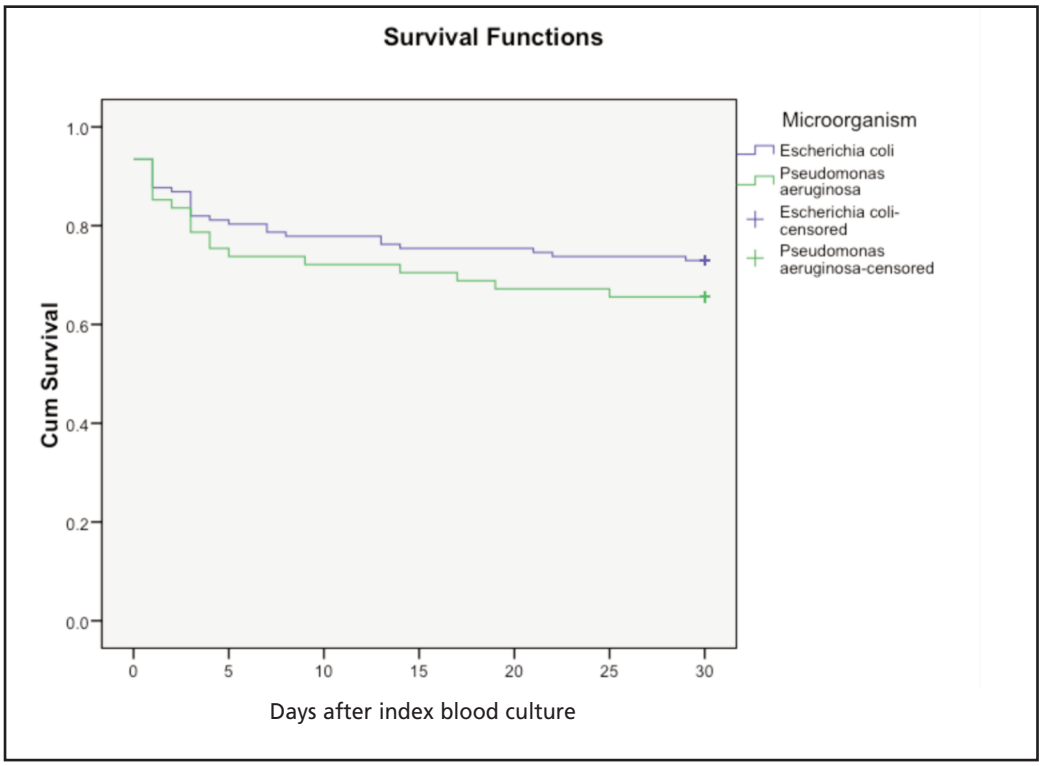


**Fig. 1:** Kaplan-Meier survival curve for patients with *Pseudomonas aeruginosa* versus *Escherichia coli* bacteraemia.

Additionally, there was a significant difference in term of empirical antibiotics prescription where pseudomonal case subjects recorded higher rates of inappropriate empirical antibiotics (50.8% vs. 22.1 %), delayed switching to appropriate antibiotics (23.0% vs. 12.3%) and inappropriate definite antibiotics (19.7% vs. 7.4%) as demonstrated in Table I. Among the 21 subjects who received inappropriate definite antibiotics, the reasons of not switching to appropriate antibiotics were as follow: subjects improved with initial inappropriate empirical antibiotics (10 subjects), blood culture reports not reviewed (4 subjects), subjects died before availability of blood culture (5 subjects) and subjects took at-own-risk discharge (2 subjects).

Interestingly, the 30-day mortality rate was lower among pseudomonal subjects who received inappropriate empirical antibiotic with subsequent non-delayed or delayed switching compared to those who received appropriate empirical antibiotics (0.0% vs. 21.4% vs. 36.7%; $p$=0.087). Further analysis revealed that the later had the highest median SOFA score compared to subjects who received inappropriate empirical antibiotic with subsequent non-delayed or delayed switching (6.5 vs. 4.0 vs. 4.5; $p$=0.226). In contrast, a higher 30-day mortality rate among *E. coli* subjects was observed in the cohort who had non-delayed switching to appropriate antibiotics (66.7%) and who had inappropriate definite antibiotics (33.3%) as shown in Table II.

The in-hospital mortality rate (32.8% vs. 23.0%; $p$=0.154) and 30-day mortality rate (34.4% vs 27.0%; $p$=0.302) were higher among *Pseudomonal* group. The 30-day survival rates, stratified according to types of organisms were presented in Kaplan-Meier curve as illustrated in Figure 1. It demonstrated 34.4% and 27.0% mortality rate in *P. aeruginosa* group and *E. coli* group respectively. The former group had a lower survival probability of 30-day survival.

**Risk Factors of Community Onset *Pseudomonas aeruginosa* bacteraemia**

Multiple logistic regression analysis identified following as independent predictors of CO PB: recent admission in the last three months (Adj. Odds Ratio, OR=4.06; 95%CI: 1.73, 9.53), regular haemodialysis (Adj. OR=44.13; 95%CI: 5.36, 363.27), immunosuppressive therapy in the past 30 days (Adj. OR=13.82; 95%CI: 1.41, 135.43), chronic wound/pressure sore at presentation (Adj. OR=4.49; 95%CI: 1.32, 15.32) and indwelling urinary catheter at presentation (Adj. OR=7.17; 95%CI: 1.30, 39.49). Whilst older age was identified as a negative predictor of CO PB (Adj. OR=0.97; 95%CI: 0.94, 1.00) as shown in Table III.

**30-Day Mortality Predictors of Community Onset Gram Negative Bacteraemia**

Multiple logistic regression analysis identified following as 30-day mortality predictors of community onset gram negative bacteraemia: older age (Adj. OR=1.06; 95%CI: 1.02, 1.10), underlying solid tumours (Adj. OR=7.80; 95%CI: 1.91, 31.82), neutropaenia at presentation (Adj. OR=23.10; 95%CI: 1.62, 328.88), in-patient mechanical ventilation (Adj. OR=14.43; 95%CI: 3.54, 58.80) and in-patient nasogastric tube insertion (Adj. OR=10.88; 95%CI: 3.49, 33.92). Interestingly, receipt of inappropriate empirical antibiotics which was switched later (delayed and non-delayed switching) was identified as the negative predictors of mortality in comparison with receipt of appropriate empirical antibiotics (Adj. OR=0.2; 95%CI: 0.05, 0.83) as shown in Table IV.

## DISCUSSION

Currently, PB is proven to be a rare occurrence as only 61 episodes of CO PB were recorded over a span of five years period in two district hospitals in Malaysia. Nevertheless, PB still poses an existential threat as it is associated with high morbidity and mortality.[1,6,7] In spite of this, standard of care for hospital acquired infection, which entails broad spectrum antibiotics with anti-pseudomonal coverage cannot be applied to all patients presenting with community onset gram negative bacteraemia, especially in the setting where pseudomonal infections are only few and far between. Restrictive use of anti-pseudomonal antibiotics is vital as rampant use of such broad-spectrum antibiotics would lead to selective pressure of the ambient microorganism, which would ultimately lead to the nascence and spread of multi-drug resistant organism.[5]

Identification of predictive factors for PB is crucial as it enables judicious use of anti-pseudomonal antibiotics among at risk population. Our data revealed that recent admission, regular haemodialysis, immunosuppressant use, chronic wound and indwelling urinary catheter to be significantly associated with PB. These results corroborated with previous the study by David et al., which was conducted in two district hospital in the United Kingdom (UK) that bears close resemblance to our population.[3] Yet, haematological malignancy, solid tumours and neutropenia, which are well established risk for PB was not associated with increased risk of pseudomonal infection in this report.[2,8] The foremost cause of this discrepancy would be that previous studies were conducted in tertiary hospital where there was a high burden of haemato-oncological subjects.

The absence of sporadic multi-drug resistant *P. aeruginosa* in this report strengthens our conviction that empirical antimicrobial therapy that encompass either third generation cephalosporin or piperacillin/tazobactam are generally adequate in district setting. Another marked observation that emerges from this report was that nearly half of the pseudomonal cohort had pre-existing chronic renal disorder with an increased trend towards haemodialysis treatment during the hospitalisation. Considering this, we caution the use of aminoglycoside in PB due to its nephrotoxicity side effects and highlight the importance of close renal function monitoring.

In previous published studies, the source of infection is determined based on clinical grounds and concomitant growth from the causative system is not mandated.[2,3,9] It is intriguing that majority of gram-negative bacteraemia did not have demonstrable concomitant cultures from other sources. The numbers could be partly contributed by subjects with hepatobiliary tract infection, which only occurred in *E. coli* cohort as attempt of culture collection from the causative organ system are deemed as both high risk and implausible. Notwithstanding, concomitant yield from sputum samples and urine samples remained low despite accounting for majority of the sources. Therefore, it is reasonable to suggest that a negative microbial work-up from non-blood-based

culture does not preclude the presence of blood stream infection among the at-risk populations. We recommend blood culture as the gold standard in ruling out blood stream infections in patients who present with sepsis, especially those with aberrant immune system.

The preponderance of pre-existing chronic kidney disease or end stage renal failure among the pseudomonal cohort explains the increased rate of profound anaemia, blood product transfusion and haemodialysis among the case subjects. Although anaemia was more commonly seen among the pseudomonal cohort, our numbers were not significant enough to draw a meaningful conclusion, yet this observation sheds potential research interest exploring the relationship between anaemia, septicaemia, and potentially poorer clinical outcome.

Interestingly, despite the high burden of morbidity and excess mortality in case subjects, PB was not identified as the predictors of mortality in comparison to *E. coli* bacteraemia. In fact, this report identified clinical features like older age, pre-existing solid tumours, neutropaenia at presentation, mechanical ventilation requirement and nasogastric tube insertion to be the risk factors of gram-negative bacteraemia mortality. We can conceivably hypothesize frailty and life-shortening chronic conditions such as malignancy have a major influence on the outcome of survival. These demographic and clinical features are not incorporated in SOFA scoring, despite contributing significantly to increased mortality.

The intuitive concept about appropriate empirical antibiotics would lead to better survival in gram negative bacteraemia was not substantiated in this report.[10] On the contrary, we identified administration of inappropriate empirical antibiotics, which was switched later to be a predictive factor for survival. This contradictory observation emphasizes that appropriate empirical antibiotics is not the sole determinant of sepsis survival as this involves an inter-play of multiple factors. In our opinion, we emphasize that the enthusiasm of choosing appropriate empirical antibiotics should not overshadow the importance of timely fluid resuscitation, sepsis source control, nutrition therapy, as well as judicious use of blood products and life support in ICU which deserve equal attention.[11]

Inevitably, due to the retrospective design, missing data in this study could lead to underestimation or missing out certain significant variables. The upshot of this study is that it represents the first study examining CO pseudomonal bacteraemia that was conducted Malaysian district hospitals. Also, the data were collected pro forma by trained data abstractors who were experienced clinicians, thus reducing the likelihood of data collection error.

## CONCLUSION

In summary, the clinical characteristics of pseudomonal bacteraemia in this study differ from previous research that have been undertaken in tertiary hospitals. Interestingly, observations from our data did not support the preconceived notion that *P. aeruginosa* bacteraemia and delayed appropriate antibiotics were more commonly associated with increased odds of mortality. In fact, host factors display a higher influence on the mortality rate as opposed to type of infections and timeliness of antibiotics. Lastly, we recommend judicious use of anti-pseudomonal antibiotics among at risk groups keeping in mind that community onset pseudomonal bacteraemia remain a rare condition in district setting.

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## 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/ P20-28 (6) dated 16 Jan 2020. NMRR ID: NMRR-19-3400-51985

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