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Pseudomonas aeruginosa bacteraemia in burns patients: Risk factors and outcomes

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ABSTRACT

Introduction: We aimed to identify the risk factors for, and outcomes of *Pseudomonas aeruginosa* bacteraemia in adult burns patients.
Method: All adult burns patients who developed a Gram-negative bacteraemia over a period of 7 years were included. Retrospective data analysed included patient demographics, organisms cultured, antibiotic susceptibility patterns, isolation of *P. aeruginosa* in non-blood isolates, treatment, length of stay and mortality.
Results: Forty-three patients developed a Gram-negative bacteraemia over the study period, 12 of whom had *Pseudomonas* bacteraemia during the course of their admission. In eight patients (18.6%) *P. aeruginosa* was the first Gram-negative isolated. The only factor predicting *P. aeruginosa* bacteraemia as a first episode (compared to another Gram-negative) was prior isolation of *Pseudomonas* at other sites (wound sites, urine or sputum). Overall length of stay was less in patients who developed *P. aeruginosa* as a first episode, mainly because of increased mortality in this group. Prior non-blood isolates of *P. aeruginosa* could have correctly predicted the sensitivity pattern of the strain of *P. aeruginosa* organism in 75% of patients who did not receive appropriate initial antibiotics.
Conclusion: Prior colonisation with *P. aeruginosa* predicts *P. aeruginosa* in blood cultures, as opposed to other Gram-negative bacteria. Clinicians should have a high index of suspicion for *P. aeruginosa* bacteraemia where a septic burns patient has a prior history of non-blood *P. aeruginosa* cultures. Empirical antibiotic regimes based on the antibiotic-sensitivity patterns of previous non-blood *P. aeruginosa* isolates in each patient should be given at the time blood cultures are taken.

1. Introduction

Infections are a major cause of morbidity and mortality in burns patients [1,2]. *Pseudomonas* is generally the most frequently isolated Gram-negative bacterium [1,3] and most serious cause of life-threatening infections [4]. The devitalised tissue and moist environment of burns provide an ideal environment for colonisation and infection with *Pseudomonas aeruginosa* [5],

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further exacerbated by alterations of immune function in burns patients [6]. Nosocomial *P. aeruginosa* infection is associated with increased mortality and morbidity (length of stay, days on ventilation, and number of operations) [1,2].

Delayed use of appropriate antimicrobial agents increases mortality in septic patients [7]; despite this as few as 50% of patients receive effective antibiotics within an appropriate time frame [7]. Therefore where a patient is septic, it may be useful to determine the likelihood of whether *Pseudomonas* is the cause before the results of blood cultures are available. Few studies compare the risk factors for serious *P. aeruginosa* infection to that for other Gram-negatives.

We performed a retrospective review of all patients admitted to the Victorian Adult Burns Service, Australia who developed a Gram-negative bacteraemia. Our goals were to describe the incidence, risk factors and time-course of *P. aeruginosa* bacteraemia and to determine whether appropriate antibiotics have been prescribed for these patients in a timely manner. We examined the risk factors for, and outcomes of, Gram-negative bacteraemia caused by *P. aeruginosa* compared with other Gram-negative bacteria.

2. Materials and methods

2.1. Setting

The Victorian Adult Burns Service (VABS) is a state-wide adult burns service located at The Alfred Hospital, a 300-bed university affiliated tertiary referral centre in Melbourne, Australia.

2.2. Ethics

Approval was obtained from our hospital's human research and ethics committee.

2.3. Data collection

A retrospective chart review (medical records, VABS and microbiology databases) was performed on all patients admitted to the VABS between January 2001 and February 2008. All patients with a Gram-negative bacteraemia had demographic data collected, including age, gender, percentage of total body surface area burned (%TBSA), percentage of full thickness body surface area burned (FTSA%), site of burn, hospital and intensive care unit (ICU) length of stay (LOS), presence of inhalation injury and selected co-morbidities (renal failure, diabetes mellitus).

Other clinically relevant markers were also collected: date of the first Gram-negative organism cultured, antibiotic used during patient care prior to isolation of Gram-negative bacteraemia, and the isolation of *P. aeruginosa* in wound, urine, sputum and broncho-alveolar lavage cultures. Antibiotic susceptibility was measured for each blood culture isolate by the same agar dilution method throughout the study period according to standard CLSI criteria [8].

The unit policy of the VABS is to collect blood cultures routinely if a patient develops a fever of $>38.5\ ^{\circ}C$ (101.3 °F), or on other clinical suspicion of sepsis following assessment of a combination of clinical factors including, but not limited to, tachycardia, hypotension, diaphoresis, fever, raised inflammatory markers, platelet dysfunction or prior positive wound or non-wound cultures. Since 2002, the VABS has implemented a protocol whereby patients with burns or complex wounds have at least weekly surveillance swabs. Surgical burn wound excisions are also routinely send to microbiology.

Each bacteraemia was counted once irrespective of the number of positive blood cultures within 7 days; however, if the same organism grew again more than 7 days later it was counted as a new episode. *P. aeruginosa* bacteraemia was considered to be a contributive factor towards a patient's mortality based on retrospective clinical assessment of patient records by two independent clinicians, and with regard to the time-course between isolation of a positive blood culture with *P. aeruginosa* and the patient's death (<2 weeks).

2.4. Statistical analysis

All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Patients who had a first-episode positive Gram-negative blood culture with *P. aeruginosa* (the "*Pseudomonas*" group) were compared to those patients with other first-episode Gram-negative bacteraemia (the "Comparator" group). In order to ensure the two groups were relatively well matched, and to avoid the confounding effects of prior episodes of bacteraemia, we limited our comparative analyses to first episodes of bacteraemia only in both groups. A comparison between groups was performed using the Mann–Whitney *U*-test for nonparametric continuous variables or the Student *t*-test for parametric continuous variables and Fisher's exact test for categorical variables. Continuous variables are reported as mean ± SD or median (inter-quartile range) and categorical variables as proportions. A two-sided *p*-value of 0.05 was considered to be statistically significant.

3. Results

3.1. Patient demographics and characteristics

A total of 1074 patients were admitted to VABS from January 2001 to February 2008 inclusive; 43 patients developed one or more Gram-negative bacteraemia. Twelve patients developed *P. aeruginosa* bacteraemia during the course of their admission, eight of these doing so as a first bacteraemic episode. Of patients developing Gram-negative bacteraemia, 56% were men, with a mean age of 41.6 years (range 17–79 years); most (40/43, 90%) had been, or currently were in ICU. They had a median %TBSA of 40 (range 14–90%); most burns were due to flames (41, 95.4%); inhalation injury was relatively common (28; 65.1%); and the upper limbs, head/neck and chest were the most commonly burned sites. Patient demographic details are outlined in Table 1. No significant demographic differences between "*Pseudomonas*" and "Comparator" (i.e. other non-*P. aeruginosa* Gram-negative bacteraemia) groups were identified.

3.2. Type and time-course of Gram-negative bacteraemia

Of the 43 first episodes of Gram-negative bacteraemia, 17 (39.5%) were due to *Acinetobacter baumannii* and eight (18.6%)

Table 1 – Demographic and mortality data of *Pseudomonas* and Comparator groups.

Demographic/mortality	*Pseudomonas* group $n = 8$	Comparator group $n = 35$
	Median (IQR)	Median (IQR)
FTSA%	17.5 (13–22)	25 (12–50)
TBSA%[a]	42.4 (9.6)	49.3 (3.8)
Age (years)[a]	51.3 (6.8)	39.4 (2.5)
Male	5 (62%)	19 (54%)
Female	3 (38%)	16 (46%)
Inhalation injury	5 (62%)	23 (65%)
Renal failure	0 (0%)	3 (8%)
Diabetes mellitus	0 (0%)	1 (2%)
ICU admission	8 (100%)	32 (91%)
Mortality	3 (37%)	4 (11%)

[a] Where data was best using parametric measures, it is expressed as mean (standard deviation).

due to *P. aeruginosa*; other organisms were much less frequent (Table 2). Cases of *A. baumannii* mainly occurred from October 2002 to April 2004. In contrast, there was no temporal clustering of *P. aeruginosa* cases.

Median time to the development of bacteraemia was not different between the ''*Pseudomonas*'' group (18 days post-burn (IQR 11–28.5)) and the ''Comparator'' group (15 days (IQR 8–23)). Two of the eight *Pseudomonas* patients went on to develop a second *P. aeruginosa* bacteremia. Amongst the ''Comparator'' group, four patients (9.3%) subsequently went on to develop a bacteraemia with *P. aeruginosa* during their admission.

The location of the patient when the bacteraemia occurred was the same in both the ''*Pseudomonas*'' group (75% in ICU) and the ''Comparator'' group (74% in ICU).

Four patients developed *P. aeruginosa* bacteraemia after another prior bacteraemia, resulting in a total of 12 *P. aeruginosa* bacteraemias in total in our population.

3.3. *Presence of colonisation of Pseudomonas aeruginosa in non-blood cultures*

Overall, 114 patients admitted to the VABS over the study period had at least one positive *P. aeruginosa* non-blood culture. Of these eight went on to develop a *Pseudomonas* bacteraemia at some stage (seven as their first episode, one as a subsequent episode of bacteraemia); 106 patients did not go on to develop a *P. aeruginosa* bacteraemia at any stage during the course of their admission. Four *P. aeruginosa* bacteraemias occurred without prior isolation of *P. aeruginosa* at another site.

In patients with first episodes of Gram-negative bacteraemia, prior isolation of *Pseudomonas* was highly suggestive of this being the cause: seven of the eight patients in the ''*Pseudomonas*'' group (87.5%) had *P. aeruginosa* cultured in another site prior to the blood; but only two of the 35 patients in the ''Comparator'' group had *P. aeruginosa* isolated prior to development of their bacteraemia. Prior positive isolates of *P. aeruginosa* from wound, sputum and urine cultures were each independently found to be significantly related to the development of a *P. aeruginosa* bacteraemia as a first episode in comparison to developing a bacteraemia from another Gram-negative ($p < 0.05$).

Time for development of a positive *P. aeruginosa* blood culture isolate from the first episode of a *P. aeruginosa* non-blood culture isolate was a median of 4 days (range 0–107 days).

Table 2 – Distribution of Gram-negative organisms isolated as a first-episode bacteraemia.

Organism	No. of patients involved in (%) $n = 43$
Acinetobacter baumannii	17 (39.5)
Pseudomonas aeruginosa	8 (18.6)
Escherichia coli	4 (9.3)
Klebsiella pneumonia	3 (7.0)
Burkholderia cepacia	2 (4.7)
Enterobacter cloacae	2 (4.7)
Other	4 (9.4)

3.4. *Mortality outcomes*

Overall mortality of patients with Gram-negative bacteraemia was 16.3% ($n = 7$): 37.5% of patients who developed a first-episode *P. aeruginosa* bacteraemia died ($n = 3$) compared with 11% in the Comparator group ($n = 4$). Of patients who developed *P. aeruginosa* bacteraemia at any stage in their admission ($n = 12$), the mortality rate was 33% ($n = 4$) in comparison with those patients who developed a non-*Pseudomonas* Gram-negative bacteraemia at any stage in their admission (i.e. not necessarily as a first episode) for whom the mortality rate was 9.6% ($n = 3$). *P. aeruginosa* bacteraemia was considered to be a contributing factor to the deaths of two patients as determined by retrospective clinical assessment of patient records by two independent clinicians, and with regard to the time between isolation of a positive blood culture with *P. aeruginosa* and the patient's death.

3.5. *Length of stay of patients*

The median LOS in hospital for all patients was 75 days [IQR 42–124]; it was significantly shorter for those in the ''*Pseudomonas*'' group (37.5 days [IQR 29–66]) than the ''Comparator'' group (83 days [IQR 46–147], $p = 0.014$). The time in hospital prior to the first bacteraemia was not different between the two groups; the difference in overall LOS in hospital was mainly due to a shorter LOS after the first bacteraemia in the pseudomonas group ($p = 0.016$): if patients who died were excluded, the overall LOS after the first bacteraemia in the

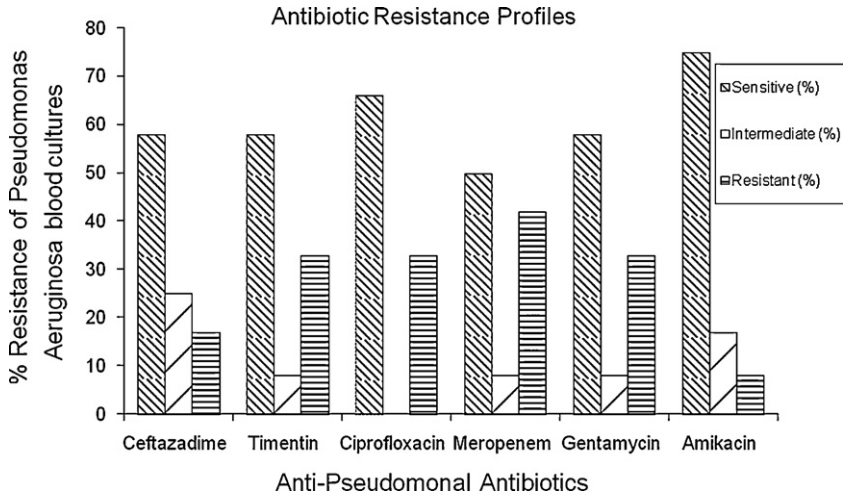

Fig. 1 – Antibiotic resistance profiles.

''*Pseudomonas*'' group was 38 days [IQR 31-85] as opposed to the ''Comparator'' group which was 75 days [IQR 45.5–126].

Excluding patients who died overall, length of stay was similar in patients who developed a *P. aeruginosa* bacteraemia at any time (83 days [IQR 34.5–85]) compared to patients who developed another Gram-negative bacteraemia only (77 days [IQR 48–142.3]).

3.6. *Number of procedures undertaken and antibiotic prophylaxis used prior to first episode of Gram-negative bacteraemia*

A total of 32 patients underwent an average of 1.2 operative procedures (IQR 1–3) during the course of their treatment. There were no differences in number of procedures or use of intra-operative antibiotic between the two groups (data not shown).

3.7. *Antibiotics used and antibiotic resistance patterns between ''Pseudomonas'' and ''Comparator'' groups*

There were no differences between groups in terms of prior use of antibiotics, any particular antibiotic class used, or duration of antibiotic use (data not shown). *Pseudomonas* isolates were more likely to be sensitive to gentamicin ($p = 0.015$) and timentin ($p = 0.035$) than isolates from the ''Comparator'' group.

3.8. *Time-course of antibiotic administration in all P. aeruginosa bacteraemia cases*

The antibiotic resistance profiles of the 12 isolates causing *P. aeruginosa* bacteraemia including those that occurred as a first-episode bacteraemia (the ''*Pseudomonas*'' group), and those that occurred as a subsequent bacteraemia (the ''Comparator'' group) are depicted in Fig. 1. Organisms were most resistant to meropenem (42%), followed equally by gentamicin (33%), ciprofloxacin (33%) and timentin (33%).

Of these 12 patients, eight had anti-Pseudomonal antibiotics administered empirically in the 24-h period after the blood cultures were taken, but before results were known. Only four were given anti-Pseudomonal antibiotics which were effective against that strain of *P. aeruginosa*, none of these patients died (Table 3). Of these four patients, two had never grown a positive *P. aeruginosa* non-blood culture previously

Table 3 – Mortality outcomes and inappropriate initial antibiotic treatment.

Patient	Age	%TBSA	FTSA%	Inhalation injury	Death	Appropriate empiric antibiotics	Predictability of resistance	Days until appropriate antibiotic Rx	Contributing mortality
1	31	60	30	Yes	No	Yes	No	N/A	N/A
2	78	30	15	Yes	No	Yes	Yes	N/A	N/A
3	53	20	10	No	No	Yes	Yes	N/A	N/A
4	42	35	20	Yes	No	Yes	No	N/A	N/A
5	24	90	35	Yes	Yes	No	Yes	N/A	Yes
6	53	18	13	No	Yes	No	Yes	1	No
7	79	36	24	Yes	Yes	No	Yes	1	No
8	31	90	78	Yes	No	No	No	2	N/A
9	17	80	60	No	No	No	Yes	5	N/A
10	36	80	20	Yes	No	No	Yes	1	N/A
11	44	30	13	No	No	No	Yes	4	N/A
12	24	80	70	Yes	Yes	No	No	2	Yes

and therefore it is impossible to say whether previous growth might have influenced the decision to treat with that particular effective antibiotic.

Of the eight patients who did not receive effective initial antibiotics (four given no initial antibiotics, four given ineffective antibiotics), four died: the two patients whose deaths were considered to be contributed to by *P. aeruginosa* bacteraemia were both in this group. Of these two, one patient received inappropriate empiric antibiotics but resistance could have been predicted based on prior isolates. The second patient also received inappropriate empiric therapy but resistance was not predictable from prior isolates. The median time from requesting blood cultures until administration of antibiotics which were effective against the strain of *P. aeruginosa* causing bacteraemia was 2 days (range 1–5 days). An appropriate antibiotic could have been selected at the time the blood culture was taken in six of these eight patients if prior sensitivities of non-blood isolates of *P. aeruginosa* had been considered (Table 3).

4. Discussion

Only the prior isolation of *Pseudomonas* in a patient independently predicts the cause of bacteraemia being due to *Pseudomonas* rather than another Gram-negative. Around 10.5% of patients with *P. aeruginosa* at another site went on to develop a *P. aeruginosa* bacteraemia ($n = 12$). Seven of the eight patients who developed a first-episode *P. aeruginosa* bacteraemia had at least one prior *P. aeruginosa* non-blood culture, compared to only two of the 35 patients whose first bacteraemia was due to another Gram-negative. This was independently true for each of wound, urine and sputum culture, even with our small population size.

Prediction of *P. aeruginosa* bacteraemia may allow for implementation of prevention strategies or earlier appropriate therapy. Based on our findings, where a first-episode Gram-negative bacteraemia is suspected, prior *P. aeruginosa* in any other site had a positive predictive value in our population of 78% for the bacteraemia also being due to *Pseudomonas*; the negative predictive value, if *Pseudomonas* had not been found at any other site, was 97% against *Pseudomonas* being found in a blood culture.

Patient demographics (age, gender) and clinical factors (TBSA% burned, FTSA% burned, type and site of burn, presence of inhalation injury, admission to another health service for >6 h prior to transfer, presence of co-morbidities such as diabetes and renal failure) do not help predict Pseudomonal bacteraemia, suggesting that these factors are unlikely to play a specific role in the aetiology of serious *P. aeruginosa* infection compared with other Gram-negatives.

Gram-negative organisms occur more frequently beyond the first week post-burn [2,8,9], a finding supported by the results of this study. The average time to isolation of *P. aeruginosa* was slightly higher than that of other Gram-negatives, but this relationship was not statistically significant.

The most common Gram-negative organism causing bacteraemia in our burns population was not *P. aeruginosa*, but *A. baumannii*, present in seventeen patients (39.5%) as an initial episode. These predominantly occurred in a short time frame, reflective of an outbreak of this organism at our hospital from late 2002 to 2004 [10]. In the years outside this outbreak, *P. aeruginosa* was the most common cause of Gram-negative bacteraemia.

More patients with *P. aeruginosa* as an initial episode died (37.5%) compared with other Gram-negatives (11%); this difference was not significant, possibly due to the low numbers. Notwithstanding the high proportion of *Acinetobacter* bacteraemia (said to have a high mortality in this population [10]), the mortality rates of *P. aeruginosa* bacteraemia seems high. It is, however, at the lower end of the range described in the literature [11], possibly reflecting advances in burn care and treatment of sepsis.

The length of stay in hospital of patients with a first-episode *P. aeruginosa* bacteraemia was significantly less than in our ''Comparator'' group, a reflection of their higher mortality. Although other studies have noted that infection with *P. aeruginosa* is associated with an increased length of stay in intensive care units, this was not true in our patients.

Use of antibiotics prior to bacteraemia did not differ between the two population groups: hence prior antibiotic use cannot be used to predict risk of *P. aeruginosa* bacteraemia. However there was a difference in the antibiotic-sensitivity pattern of the *P. aeruginosa* isolates versus the other Gram-negatives—but in favour of the *P. aeruginosa* which were more likely to be sensitive to ticarcillin/clavulanate and gentamicin. This is explained by an outbreak of highly resistant *A. baumannii* that occurred in our hospital over an 18-month period.

A number of studies have suggested particular antibiotics to treat resistant *P. aeruginosa* infections in burns patients [12], with mixed recommendations. Our strains of *P. aeruginosa* were considered to be more resistant to carbapenems than any other class of anti-Pseudomonal antibiotic, and therefore rather than broad recommendations, empirical antibiotic regimes should be tailored to each individual unit and may need to be reviewed regularly.

Many patients did not receive effective initial anti-Pseudomonal antibiotics. Studies have shown that a single multi-drug resistant (MDR) *P. aeruginosa* isolate can persist in the same patient for several months and cause recurrent episodes of infection [13,14]. Our study supports the view that the resistance pattern of prior isolates can help to guide antibiotic choice in 75% of patients who do not currently receive initial effective antibiotics.

Antibiotics also need to be administered promptly: a recent review of septic shock patients demonstrated a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality [7]. Of our 12 patients who developed *P. aeruginosa* bacteraemia at any time, four died. Of these, *P. aeruginosa* was considered to have been a contributing factor to mortality in two cases. Of the two patients to whom *P. aeruginosa* was considered to be a contributing factor in terms of mortality, neither were given effective anti-*Pseudomonas* antibiotics prior to the result of blood cultures becoming known.

Our study had a number of limitations. We analysed relatively small patient populations and cannot exclude small but clinically significant effects predisposing patients to *P. aeruginosa* bacteraemia. Accepted risk factors for mortality in

burns patients, such as TBSA%, FTSA% and presence of inhalation injury were not different between the ''*Pseudomonas*'' and ''Comparator'' grounds, however, given the small sample size, we cannot exclude other co-morbidities that may be significant. Larger sample sizes may reveal more significant results.

In contrast to other studies, *P. aeruginosa* was not the most common Gram-negative causing bacteraemia in our study, reinforcing the varying prevalence of this organism both between burn units, and within units over time [3,15,16]. The most prevalent organism in our population was *A. baumannii*, a finding that replicates numerous other results [1,15,17]. For this reason, the ''Comparator'' population may have been skewed by this outbreak of *A. baumannii*.

The accuracy of blood cultures in burns patients has been questioned due to the high alterations in skin flora and subsequent identification of contaminated samples [18]; however, *Pseudomonas* is an uncommon contaminant in blood cultures, and all staff in our ICU (where the majority of these bacteraemias occurred) receive training in sterile blood culture collection technique to minimise contamination.

Our policy is to send wound swabs at least weekly for patients with prolonged stays, particularly those requiring frequent operations or who have a clinically suspected wound infection. We are unable to say whether more active screening would effect the predictive value of prior isolation of *Pseudomonas*.

Prior colonisation with *Pseudomonas* independently predicts *Pseudomonas* in blood cultures, as opposed to other Gram-negative bacteria. This suggests that it is a necessary prelude in the pathogenesis of *P. aeruginosa* bacteraemia. It reinforces the importance of knowing the patients' own microbiology, as well as that of the unit in which the patient is cared for, when selecting the correct therapy for initial management of sepsis. Empirical antibiotic regimes may be more effective if they are given at the time blood cultures are taken and based on the antibiotic-sensitivity patterns of previous non-blood *P. aeruginosa* isolates in each patient. Larger scale research needs to be undertaken to validate these findings.

Conflict of interest

None declared.

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