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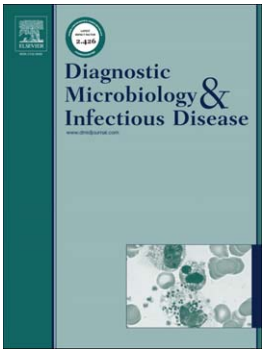

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Increased Risk of Death with Recurrent *Pseudomonas aeruginosa* Bacteremia

Running Title: Recurrent *Pseudomonas aeruginosa* bacteremia

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Abstract

This study aimed to characterise recurrent *Pseudomonas aeruginosa* blood stream infection (BSI). Positive blood cultures for *P. aeruginosa* were identified over a three year period from seven tertiary care hospitals. Patients with relapsing BSI were identified. Extensive epidemiological, clinical and outcome data were obtained. BSI relapse was found to be uncommon with nine percent of patients having a first relapse of BSI. Fourteen percent of these patients went on to have a second relapse of BSI. Significant variables associated with recurrence were the presence of a hematological malignancy or receiving recent corticosteroid therapy. Exposure to anti-pseudomonal beta-lactam therapy in the 30 days prior to the BSI was more likely in the patient with the recurrent BSI episode. Recurrence was associated with increased mortality when compared to the primary BSI episode. Knowledge of a patient's prior antibiotic therapy may be useful in ensuring effective empirical therapy in the recurrent BSI episode.

1.1 Key Words:

Pseudomonas aeruginosa, recurrent, relapse, bacteremia, mortality

1.2 Introduction

The Centers for Disease Control and Prevention found that *P. aeruginosa* accounted for 7.1% of health care acquired infections (HCAI) in the United States in 2011. It was the third most common gram negative cause of blood stream infections (BSI) [1]. This is an infection with considerable mortality with rates of up to 42% being described depending on the population studied [2]. Although primary infection has been well studied, cohort studies looking at *P. aeruginosa* BSI over the last decade have typically excluded recurrent infection episodes. Recurrent *P. aeruginosa* infection has been described in the literature in 3 patient groups: liver transplantation, human immunodeficiency virus infection (HIV) and bone marrow or stem cell transplantation patients [3-5]. In clinical practice recurrent infection is also seen outside these patient groups. This tertiary multicentre study aimed to: a. further characterise the patient in whom a recurrent *P. aeruginosa* BSI occurs; b. look at time to infection recurrence; and c. to characterise the variables that may place an individual at risk for recurrence of this infection.

1.3 Materials and Methods

1.3.1 Study design

The study was conducted at 7 tertiary care hospitals in Brisbane, Australia. The hospitals range in size from 207 to 929 beds. Together they provide a specialised and broad medical, surgical and intensive care for an urban population of 2.24 million. Positive blood cultures for *P. aeruginosa* were identified over the 3 year time period of the 1st of January 2008 to the 31st of December 2010 from the laboratories servicing the hospitals. A BSI episode was identified as the 14 day time period from the date of the first positive blood culture. Patients were excluded if they met any of the following criteria: age less than 18 years, the patient was not admitted to hospital post blood culture collection, the sentinel blood culture was not taken at a participating hospital, there was no antibiotic treatment of the blood culture isolate, the patient was transferred to another institution within 72 hours of the primary blood culture being collected, the patient's case notes could not be obtained or the patient died within seven days of the primary BSI episode. Poly-microbial BSI's or BSI episodes in which another significant pathogen was grown from a blood culture 10 days prior to 14 days post the sentinel blood culture collection with *P. aeruginosa* were not excluded.

The BSI episodes studied were divided into four groups: a. primary BSI episodes from patients who survived 7 days after the initial BSI and did not go on to have a recurrent BSI within the 3 year study period; b. the primary BSI episode in a patient who survived 7 days after the initial BSI and that went on to have recurrent infection in the 3 year study period; c. the primary relapse episode of BSI in the patient with recurrent infection; and d. any further relapsing BSI episodes in the patient that went on to have a further BSI episodes provided they survived 7 days post the preceding BSI episode. The latter group was utilised for descriptive purposes only. Ethics approval to carry out the study from all participating hospitals and laboratories was obtained.

1.3.2 Data Collection and Definitions

1.3.2.1 Assessed clinical variables

The following data was collected from all patient case notes in a retrospective fashion: age, sex, origin of infection (hospital, health-care or community acquired), patient location at the time of the sentinel blood culture collection, co-morbidities, Charlson's weighted comorbidity index (CCI), invasive medical devices in the 7 days prior to the episode, surgery in the 14 days prior to the episode, immunosuppressive therapy or blood products in the 30 days prior to the episode, source of the bacteraemia, antimicrobial therapy started from 30 days prior to

post primary bacteremia and the Pitt bacteraemia score [6, 7]. From the laboratory, details of any other blood culture isolates from 10 days prior to 30 days post the episode were obtained. In addition antibiograms of the *P. aeruginosa* isolates of interest, other sites of growth of *P. aeruginosa* within 48 hours before or after positive blood cultures for *P. aeruginosa* were recorded, as were periods of neutropenia.

1.3.2.2 Definitions

A *bacteremic episode* is defined as the 14 day time period from the date of the first positive blood culture for *P. aeruginosa.* *Recurrent infection* was defined as subsequent culture of *P. aeruginosa* outside the primary BSI episode. A *hospital acquired infection* (HAI) is defined as a positive blood culture obtained from a patient after 48 hours of hospitalisation or within 48 hours of discharge. A *healthcare associated infection* (HCAI) is defined as a positive culture obtained from a patient at the time of hospital admission or within 48 hours of admission if the BSI fulfilled any of the following criteria: 1. Is a complication of an indwelling medical device; 2. Occurs within 30 days of a surgical procedure where the BSI is related to a surgical site infection; 3. An invasive instrumentation or incision related to a BSI was performed within 48 hours before the onset of infection. If the timing of onset was longer than 48 hours there must be compelling evidence that the infection was related to an invasive device or procedure; 4. Received therapy with temporary intravenous access in the 48 hours before the onset of infection. If the timing of onset was longer than 48 hours there must be compelling evidence that the infection was related to the invasive device or procedure; 5. Associated with neutropenia ($< 0.5 * 10^9$/L) contributed to by cytotoxic therapy; or 6. The patient resided in a nursing home. A *community acquired infection* (CAI) is defined as a positive culture obtained at the time of hospital admission or within the first 48 hours after admission which does not fit the criteria for a HCAI [8]. *Underlying disease* refers to all conditions present at admission and diagnosed with up to 48 hours of the BSI. The definition of *source of infection* were defined as per modified from Centers for Disease Control and Prevention definitions [9] and line related infections were as per modified Australian Infection Control Association guidelines [8] . A line associated bacteremia was also defined as a bacteremia in the presence of a central access line in the absence of another source of infection. *Polymicrobial infection* referred to the growth of another significant bacterial isolate from the sentinel blood culture collection in which *P. aeruginosa* was also identified. *Adequate empirical therapy* referred to those patients who received an active agent against *P. aeruginosa* that was considered appropriate based on analysis of the antibiogram of the isolate causing the infection in each episode. Beta-lactam/beta-lactamase inhibitor therapy excluding amoxicillin-clavulanate, carbapenem therapy excluding

ertapenem, ceftazidime, cefepime and ciprofloxacin (intravenous) were considered potentially appropriate antipseudomonal agents. This therapy needed to start within 24 hours of the blood culture being drawn; the antibiotic had to have been administered for at least 48 hours, with the single exception of patients who died before 48 hours, who were included if death occurred after 1 complete day of therapy with the assigned regimen. *Adequate targeted therapy* referred to patients who received an active agent against *P. aeruginosa* based on the susceptibility profile of the isolate. Targeted therapy had to have started within 5 days of the blood culture being drawn and to be administered for at least 5 days. For patients who died while on targeted therapy they needed to have completed at least 1 complete day of therapy with the targeted regimen. Patients with the above criteria who continued with the same therapy that had been administered empirically once susceptibility results became available were also included. The utilisation of oral therapy was also examined by the identification of patients who made a rapid change to oral therapy (RCOT) or made a late change to oral therapy (LCOT). The RCOT cohort included any patient who received targeted therapy with the above criteria but the targeted therapy included a change to oral ciprofloxacin within the first 5 days of targeted therapy. The *LCOT* cohort included any patient who after a minimum of 5 days of targeted intravenous therapy had received at least 2 days of oral ciprofloxacin in the second 5 day phase of potential antibiotic therapy. If the patient had been rapidly changed to oral ciprofloxacin as per the RCOT cohort they were excluded from this group. Only mono-microbial BSI episodes were studied regarding the adequacy of antibiotic therapy.

1.3.3 Microbiological Methods

During the study period the blood cultures were processed by the BACTEC system (Becton Dickinson Microbiology Systems) with an incubation period of 5 days. Isolates were identified by the VITEK 2 system (bioMerieux, Balmes-les-Grottes, France). Antimicrobial susceptibility testing was performed by a microdilution method on the VITEK 2 system. Clinical and Laboratory Standards Institute (CLSI) breakpoints were used to define susceptibility or resistance to the antimicrobial agents tested.

1.3.4 Statistical analysis

The relationship between categorical variables was compared using the chi-square test or Fishers exact test. The student's t test was used for continuous variables. To identify independent risk factors for recurrent infection, variables with a p value of < 0.2 on the univariate analysis were included in a backward stepwise multivariate logistic regression model. The variable was also required to make clinical sense to be included in the model. Variables with greater than 10% of missing data were excluded from the multivariate analysis to allow inclusion

of the maximal number of patient episodes in analysis of associations with recurrent infection. To also prevent over fitting of data variables with less than 10% of the cohort having the presence of that factor were also excluded. The fit of the model was assessed by the standardized Pearson test. The analysis was done using Stata software (version 13; StataCorp LP).

1.4 Results

This study retrospectively reviewed 595 episodes of *P. aeruginosa* BSI from 541 patients in 7 tertiary care hospitals in the city of Brisbane, a capital city of Australia, over a 3 year period. BSI episodes were excluded according to pre-defined study criteria (Figure 1). This left 487 BSI episodes for analysis representing 441 patients. Over the 3 years of the study, of those patients that survived to at least 7 days post the primary infection, 41 of 441 (9%) patients went on to have a primary relapse episode of *P. aeruginosa* BSI. Of the 35 patients that survived to seven days post the first BSI relapse episode, a further 5 patients (14%) went on to have a second relapse episode of BSI. Only 2 patients went on to have a third BSI relapse and 1 patient a fourth BSI relapse. The median time to the first relapse episode of infection was 53 days with a range of 15 to 489 days. The time from the first relapse episode to second relapse episode was a median of 28 days with a range of 19 to 33 days.

The characteristics of the primary BSI in those patients that did and did not go on to have a recurrent BSI were compared (Table 1). On multivariate analysis those patients who went on to have a recurrent BSI were significantly more likely to have a hematological malignancy or to have received corticosteroids in the preceding 30 days. The characteristics of the primary and first BSI relapse episode in those patients that went on to get a recurrent BSI were also compared to look for other drivers of recurrent infection (Table 2). Lack of clinician utilisation of late oral quinolone therapy in the first relapse BSI episode was the only variable significantly different on univariate analysis between these groups (OR 0.11 (0.013-0.99), p=0.05).

The rates of antibiotic resistance in the *P. aeruginosa* BSI isolates in the primary BSI episode and the first BSI relapse episode were not found to be statistically different (Table 3). The patients with the first BSI relapse had a significantly higher rate of exposure to anti-pseudomonal beta-lactams in the 30 days prior to the BSI.

To be included in the study all patients had to survive to day 7 of the primary *P. aeruginosa* BSI episode. Of the patients that survived the primary infection and went on to have a first relapse BSI, one of the 40 patients (3%) had died at 28 days after the primary BSI. Of those patients that survived seven days of the primary infection and did not go on to have a recurrent BSI, 28 of the 378 (7%) patients in whom outcome data was available were dead at 28 days. Thus looking at all primary BSI episodes 29 of the 418 (7%) patients in whom outcome was known were dead at 28 days. In patients that went on to have a first relapse of *P. aeruginosa* BSI,

7 of the 38 (18%) patients were dead at 28 days. Of the five patients who went on to have a second episode of relapse of infection, 2 (40%) patients had died at 28 days post this BSI episode.

1.5 Discussion

This multicentre retrospective cohort study characterised recurrent *P. aeruginosa* BSI. A primary BSI relapse occurred in 9% of the cohort that survived to seven days post the primary BSI. Of the 35 patients that survived to 7 days post the first episode of BSI relapse, 14% of these patients went on to have a second episode of BSI relapse over the three year time period studied. The BSI's were predominantly hospital acquired and the most common source was a line associated infection. The time to onset of the first episode of BSI relapse was highly variable. Statistically significant variables associated with BSI recurrence were the presence of a hematological malignancy or having had corticosteroid therapy in the preceding 30 days. The rate of mortality at 28 days post BSI was higher the greater the number of relapsing BSI episodes.

Mylotte et al prospectively studied recurrent gram negative bacteremia at a single centre. Recurrent gram negative BSI occurred in 9.8% of the cohort. There were 13 (17.5%) secondary episodes of gram negative infections caused by *P. aeruginosa* in the study [10]. More recently, Al-Hasan et al looked retrospectively at recurrent gram negative BSI in a population based study. *P. aeruginosa* accounted for 7% of the BSI's. They found a cumulative incidence rate of recurrence of all gram-negative infections after 1, 5 and 10 years of the initial episode was 5.5%, 9.2% and 14.6% respectively [11]. In both studies, the primary and relapsing BSI did not have to be caused by the same gram negative bacteria. In our study, a first BSI relapse occurred in 9% of the cohort that survived to seven days post the primary BSI. Of those patients that survived to 7 days post the first BSI relapse, there was a slightly higher rate of relapse, with 14% of this group having a further BSI.

Corticosteroid therapy in the preceding 30 days and a hematological comorbidity placed an individual at risk for recurrent BSI on multivariate analysis. The occurrence of primary *P. aeruginosa* BSI infections in the hematology population is well described [12-14]. High rates of corticosteroid use were also described in the *P. aeruginosa* primary BSI cohort described by Joo et al [15]. Thus these two variables place an individual at risk for not only a primary BSI but also for its recurrence. Although a vascular catheter source was the most common source in the first relapse of BSI, it was not significantly associated with recurrent infection. This is in contrast to the recurrent all-cause gram negative bacteremia study by Wendt et al [16]. This may reflect a practice of appropriate line removal in the setting of a primary *P. aeruginosa* BSI. Neutropenia has been found to be a risk factor for primary BSI in a number of patient groups including those receiving chemotherapy and those patients with compromised bone marrow function [17]. In our cohort neutropenia was also not found to

be significantly associated with patients that went on to get a recurrent BSI. We did not find the adequacy of empirical or targeted antibiotic therapy to be significantly different between those patients that did and did not go on to have a recurrent BSI.

Haki et al looked at antimicrobial susceptibility data that was available for 8 of the 10 cases of *P. aeruginosa* BSI recurrence from their stem cell transplantation cohort. In 3 cases increasing antimicrobial resistance was seen [5]. Although we saw increased rates of resistance in the first relapse BSI patient group, this did not reach statistical significance. Bhat et al showed that in their retrospective cohort of ICU patients with a *P. aeruginosa* isolate that was resistant to piperacillin-tazobactam or cefepime, that the patient was more likely to have received these antibiotics in the month prior to the *P. aeruginosa* infection or to have had a gram-negative bacillus resistant to these antibiotics isolated in the month prior to the *P. aeruginosa* infection [18]. We found that the group of primary BSI relapse patients was significantly more likely to have received anti-pseudomonal beta-lactams in the preceding 30 days. The small number of BSI episodes in our study may be the reason why we were not able to show significantly increased rates of resistance in the relapsing BSI episodes in light of this exposure. Knowledge of recent antibiotic therapy received by a patient would seem important in choosing appropriate empirical therapy for the patient with the relapsing BSI.

Al-Hasan et al in their recurrent gram negative BSI study found that mortality rates of first and second gram negative BSI episodes were 10% and 11.3% [11]. Our study found that as the number of recurrent BSI's increased the rate of patient death at 28 days post the recurrent BSI also increased. Supporting our finding, Hakki et al found that in their hematopoietic stem cell transplantation population, infection attributable mortality after the primary BSI was 35.8% and after BSI recurrence was 60% [5].

The limitations of this study are that it is retrospective and may have hidden biases. In addition recurrent *P. aeruginosa* BSI is uncommon and thus the study had limited power. It would have been ideal to obtain data on vascular catheter retention rates however this was poorly documented in patient notes. Finally molecular typing of the isolates discussed would have allowed further insights into BSI recurrence.

1.6 Conclusions:

In conclusion this multicentre retrospective cohort study found that a recurrent *P. aeruginosa* BSI is uncommon. Recurrence is significantly associated with a hematological co-morbidity and corticosteroid use in the preceding 30 days. Those patients that survive a first BSI relapse of *P. aeruginosa* have an even higher risk of a further relapse of infection. Recurrence is associated with increased mortality when compared to the primary BSI episode. Knowledge of a patient's prior antibiotic therapy may be useful in ensuring an active antibiotic against the BSI in an episode of BSI relapse.

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1:10 Figure 1: Study participant flow chart

1.11: Table 1: Comparison of the significant patient and BSI characteristics of the primary BSI episode of those patients that did and did not go on to have a BSI relapse

1.12 Table 2: Patient and BSI isolate characteristics of the primary BSI and the first episode of BSI relapse in the host who had a recurrent *P. aeruginosa* BSI

1.13 Table 3: Comparison of antimicrobial resistance and antimicrobial exposure in the primary and first relapse BSI episodes

Table 1

Variable	Primary BSI episode characteristics in a patient that has a BSI relapse (n=40)	Primary BSI episode characteristics in a patient that does not have a BSI relapse (n=400)	Univariate analysis OR (CI)	p value	Multivariate analysis OR (CI)	p value
Age, mean (range in years)	62 (25-88)	64 (19-94)	0.99 (0.97-1.01)	0.46		
Male, n (%)Male, n (%)	20 (50)	235 (59)	0.70 (0.37 - 1.34)	0.29		
Hospital acquired acquistion	22 (55)	256 (64)	0.69 (0.36 - 1.32)	0.26		
Co-morbidities						
Central nervous system	7 (18)	79 (20)	0.86 (0.37-2.02)	0.73		
Cardiovascular system	19 (48)	221 (55)	0.73 (0.38 - 1.41)	0.35		
Pulmonary	5 (13)	107 (27)	0.39 (0.15-1.02)	0.06		
Kidney	6 (15)	65 (16)	0.91 (0.37-2.25)	0.84		
Gastrointestinal tract	9 (23)	100 (25)	0.87 (0.40 - 1.89)	0.73		
Hematological	25 (63)	114 (29)	4.18 (2.13 - 8.23)	<0.01	3.01 (1.47 - 6.17)	<0.05
Diabetes	7 (18)	80 (20)	0.85 (0.36-1.92)	0.70		
CCI, mean (score range)	2 (0-5)	2 (0-9)	1.0 (0.82-1.22)	0.97		
Medical device prior 7 days, n (%)						
Vascular catheter	31 (78)	270 (68)	1.64 (0.76 - 3.56)	0.21		
Indwelling urinary catheter	9 (23)	129 (33)	0.61 (0.28-1.31)	0.21		
Prosthesic Material	5 (13)	76 (19)	0.61 (0.23-1.60)	0.32		
Medical treatment 30 days prior						
Chemotherapy	19 (48)	105 (26)	2.52 (1.30-4.88)	<0.05		
Corticosteroids	24 (60)	112 (28)	3.83 (1.96-7.50)	<0.01	2.68 (1.31-5.44)	<0.05
Neutropenia prior 14 days	11 (28)	81 (20)	1.50 (0.71-3.12)	0.29		
Surgery 14 days prior	5 (13)	92 (23)	0.48 (0.18-1.25)	0.13		
Pitt bacteremia score, mean (score range)	2 (0-8)	1 (0-10)	1.08 (0.91-1.28)	0.84		
Ticarcillin-clavulanate	5 (13)	62 (16)	0.77 (0.29-	0.61		

resistance			2.05)			
Polymicrobial Infection or second signiifcant BSI isolate 10 days prior or 14 days post sentinel blood culture collection	9 (22)	92 (23)	0.97 (0.45-2.12)	0.94		

Table 2

	Primary BSI episode characteristics in a patient that has a BSI relapse (n=40)	First relapse BSI episode characteristics (n= 39)
Variable	**n (%)**	**n (%)**
Age, mean (range in years)	62 (25-88)	60 (25 - 87)
Male	20 (50)	20 (51)
Acquistion		
Hospital acquired	22 (55)	25 (64)
Health-care associated	15 (38)	12 (31)
Community acquired	3 (8)	2 (5)
Primary blood culture patient location		
Intensive care	3 (8)	2 (5)
Ward	23 (62)	21 (54)
Emergency Department	7 (19)	6 (15)
Outpatient Clinic	4 (11)	9 (23)
Co-morbidities		
Central nervous system	7 (18)	6 (16)
Cardiovascular system	19 (48)	18 (47)
Pulmonary	5 (13)	4 (11)
Hepatobiliary	0 (0)	0 (0)
Kidney	6 (15)	4 (11)
Urinary tract	1 (3)	1 (3)
Gastrointestinal tract	9 (23)	9 (24)
Rheumatological	2 (5)	3 (8)
Autoimmune	2 (5)	2 (5)
Skin and soft tissue	4 (10)	5 (13)
Hematological	25 (63)	24 (63)
Oncological	4 (10)	5 (13)
Diabetes	7 (18)	7 (18)
Organ or Bone Marrow Transplant	4 (10)	3 (8)
HIV	0 (0)	0 (0)
CCI, mean (range)	1 (0-5)	2 (0-5)
Medical device prior 7 days		
Vascular catheter	31 (78)	29 (76)
Indwelling urinary catheter	9 (23)	7 (18)
Prosthesic Material	5 (13)	6 (15)
Medical treatment 30 days prior	31 (78)	32 (82)

Chemotherapy	19 (48)	16 (41)
Corticosteroids	24 (60)	19 (48)
TNF blocker	0 (0)	19 (49)
Other immunosuppressive therapy	5 (13)	6 (15)
Radiation	1 (3)	1 (3)
Neutropenia at time of sentinel blood culture collection	9 (23)	16 (41)
Surgery 14 days prior	5 (13)	4 (10)
Pitt bacteremia score, mean (range)	2 (0-8)	2 (0-8)
Source of infection n (%)	35 (88)	34 (87)
Mastoiditis	0	0
Pneumonia	1	3
Intra-abdominal	0	2
Mucositis	0	0
Urinary tract infection	7	2
Line related	20	19
Musculoskeletal	0	0
Skin and soft tissue	7	3
Surgical Site Infection	0	0
Other source	0	5
Polymicrobial Infection or second signiifcant BSI isolate 10 days prior or 14 days post sentinel blood culture collection	9 (22)	8 (21)
Monomicrobial BSI Treatment (n=62)		
Adequate empirical Therapy (n=54)	20 (71)	17 (65)
Adequate targeted therapy (n=52)	23 (87)	21 (88)
Early oral Ciprofloxacin therapy (n=50)	1	0
Late Ciprofloxacin therapy (n=49)	8 (30)	1

Table 3

Antibiotic	Antibiotic resistance in first BSI episode (n = 40)	Antibiotic resistance in second BSI episode (n= 39)	Univariate Analysis
Ticarcillin-clavulanate	5 (13%)	12 (31%)	
Piperacillin-tazobactam	3/34 (9%)	5/28 (18%)	
Ceftazidime	2 (5%)	3 (8%)	
Cefepime	1 (3%)	4 (10%)	
Meropenem	1 (3%)	3 (8%)	
Any anti-pseudomonal beta-lactam	7 (18%)	13 (33%)	p = 0.11
Treatment with any anti- pseudomonal beta-lactam in 30 days prior to BSI episode	7/35(20%)	15/38 (39%)	p = 0.04

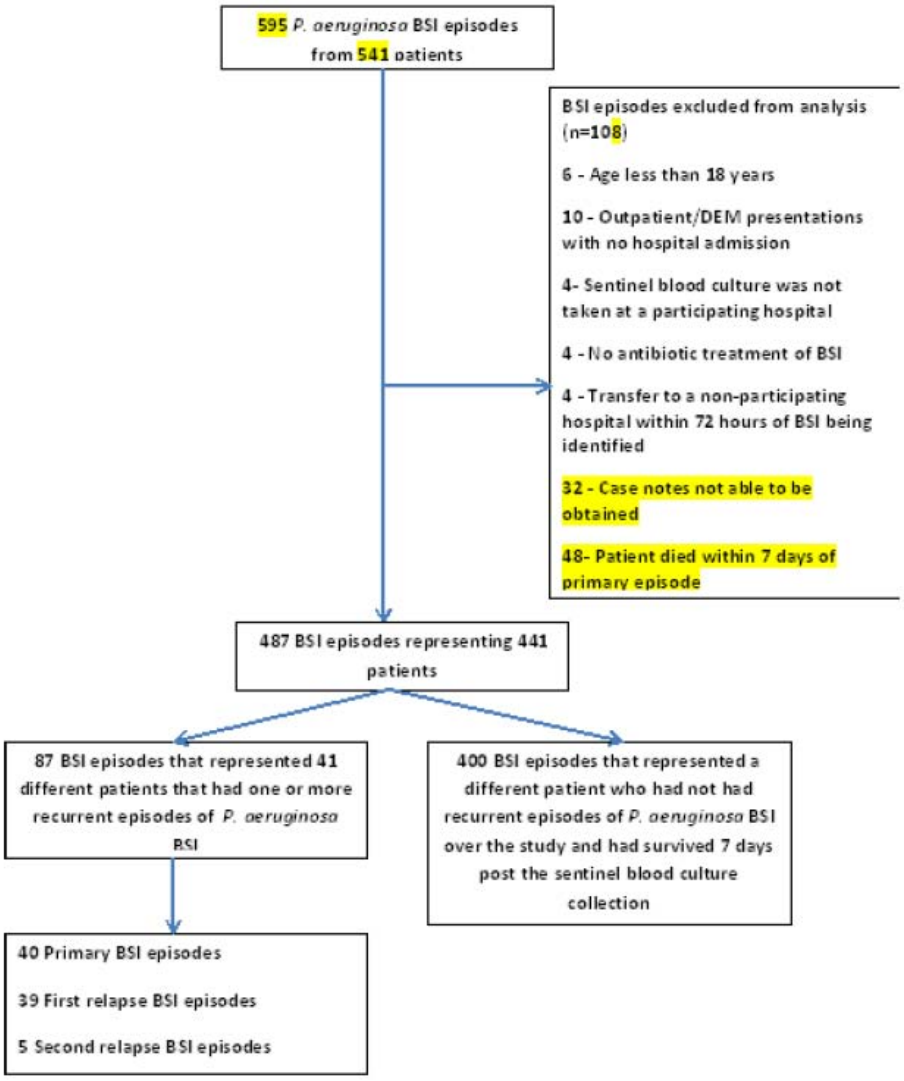

Figure 1

Highlights

- Recurrent *P. aeruginosa* blood stream infection (BSI) is uncommon
- Hematological co-morbidity and recent corticosteroid use are associated with relapse
- There is a higher risk of *P. aeruginosa* BSI relapse after a primary BSI recurrence
- Recurrence is associated with increased patient mortality
- Knowledge of a patient's prior antibiotic therapy is important for treatment choice