International Journal of Pediatric Research

Harnaen et al. Int J Pediatr Res 2015, 1:2
ISSN: 2469-5769

Case Series: Open Access

Characteristics of *Pseudomonas aeruginosa* Infection in a Tertiary Neonatal Unit

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Abstract

Pseudomonas aeruginosa is associated with fatal late onset sepsis in neonates. Despite advances in neonatal care, the management of *Pseudomonas* sepsis remains challenging especially when early and definitive therapy is critical. It is a rare cause of neonatal blood stream infections in developed countries and most studies report its occurrence in the setting of an outbreak. We present data from a busy tertiary neonatal intensive care unit in Australia, over a 12-year period. During the study period, we found 6 cases of *P. aeruginosa* blood stream infection (0.5% of total positive blood culture episodes and 4.2% of total gram-negative culture episodes). All septic (6/6) isolates were between the months of April-June and 41 out of 49 (83%) colonizations of *P. aeruginosa* were in the first 6 months of the year indicating a seasonal trend. *P. aeruginosa* sepsis was associated with high mortality (50%) and morbidity (83.3%). All isolates were sensitive to Gentamicin. *P. aeruginosa* sepsis was not associated with necrotizing enterocolitis in our unit. Our findings indicate that *P. aeruginosa* infection and colonization seems to follow a seasonal trend. Extremely low gestational age newborns (ELGANs) that have prior *P. aeruginosa* colonization may benefit from the use of dual anti-*Pseudomonal* agents.

Keywords

Pseudomona aeruginosa, Late Onset Sepsis, Colonisation, Seasonal trend

Abbreviations

BPD: Bronchopulmonary Dysplasia, DIC: Disseminated Intravascular Coagulopathy, ELGAN: Extremely Low Gestational Age Newborn, ELBW: Extremely Low Birth weight, HCW: Health Care Worker, IVH: Intraventricular Hemorrhage, IVIG: Intravenous Immunoglobulin, LOS: Late Onset Sepsis, NEC: Necrotizing Enterocolitis, NICU: Neonatal Intensive Care Unit, TPN: Total parenteral Nutrition

Introduction

P. aeruginosa is a non-fermentative, gram-negative bacillus. It is primarily an environmental organism but highly capable of surviving in a wide range of conditions [1]. In neonatal intensive care units (NICUs), it has been isolated from patient care equipment like blood gas analyzers [2], nasopharyngeal catheters [3], and breast feeding bottles [4], from the environment such as sinks [4], and; from health care workers (HCWs) [5]. It is an opportunistic pathogen as it mostly causes infection in immunocompromised hosts such as premature infants [6].

With regards to blood stream infection it is predominantly associated with late onset sepsis (LOS) [1]. In developing countries, *P. aeruginosa* is a commonly reported blood stream infective agent [7,8]. In contrast, in the developed world, *P. aeruginosa* is considered to be an uncommon cause of neonatal sepsis in the absence of an outbreak [1]. The average prevalence of *Pseudomonas* in the U.S. is 2.7% of all gram-negative late onset sepsis [9], while Gordon et al. in Australia have reported it to be up to 12.5% [10]. Most of our understanding about this deadly organism comes from epidemiological profiles reported in various outbreak settings [2,4,5]. Jefferies et al. published a systematic review of reported outbreaks of *P. aeruginosa* sepsis in neonates to identify the risk factors and environmental sources of *P. aeruginosa* [11]. Surprisingly, there have been only few attempts to study demographic, clinical and microbiological profile of *P. aeruginosa* in a non-outbreak setting [12,13]. Here we present a case series of neonates over a period of 12 years with *P. aeruginosa* sepsis from a tertiary level NICU describing the natural history of disease, the severity of involvement and associated complications. We have also tried to draw up conclusions with regards to disease profile and prognosis in this highly vulnerable age group, which will strengthen and improve our existing understanding about *P. aeruginosa* sepsis in neonates.

Materials and Methods

We conducted a retrospective audit to identify patients with *P. aeruginosa* sepsis from January 2002-December 2013 (12 years) in Monash Newborn. Monash Newborn is a suburban tertiary care NICU in Melbourne, Victoria. We excluded infants who acquired *Pseudomonas* blood isolates other than *P. aeruginosa* and those with improper documentation. The study qualified as a quality assurance project under the hospital ethics research framework. Infants were identified through the neonatal database, which is collected prospectively as part of the Australia and New Zealand Neonatal Network (ANZNN), which is maintained by dedicated staff. A different data manager from the microbiology department later confirmed these isolates from the identified cohort. The isolates include colonization on the skin and nasopharyngeal aspirates.

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Citation: Harnaen E, Doctor TN, Malhotra A (2015) Characteristics of *Pseudomonas aeruginosa* Infection in a Tertiary Neonatal Unit. Int J Pediatr Res 1:010

Received: August 25, 2015: **Accepted:** October 15, 2015: **Published:** October 19, 2015

We conducted a retrospective chart review of their admission in NICU. Maternal details like antenatal complications and results of high vaginal swabs were obtained. Demographic data such as birth weight, sex and gestational age were recorded. Infection related clinical details like date of infection, clinical signs of sepsis and shock, antibiotics used prior to and after the sensitivity pattern was available, time taken for culture to become positive, time between availability of positive culture and death, requirement of ventilation and duration of stay in nursery were recorded from available clinical notes. Laboratory investigations were noted by accessing the online pathology database system. The platelet count and immature to total neutrophil ratio were collected. The mean and median counts/ratios of patients who had blood infection were calculated. Standard definitions were used for the various clinical diagnoses. We also looked at colonization of *P. aeruginosa* from various sites during the same period.

Results and Analysis

During the study period there were 1070 positive blood cultures. Gram-negative bacilli were isolated from 141 blood cultures during this time. Six blood cultures (0.5% of total positive blood culture isolates and 4.2% of total Gram-negative isolates) from 6 different neonates were positive for *P. aeruginosa*. General and clinical characteristics of the newborns identified with *P. aeruginosa* are indicated in table 1. We excluded a case that had blood stream infection with *P. stutzeri.*

Forty-one of the 49 (83%) were isolated during the warmer months (January-June). While all of blood stream infections were recorded during the months of April to June.

Among the patients with positive blood cultures, 3 of the 6 newborns died (50% mortality) two of the 3 neonates who died had prior colonization with *P. aeruginosa* in their skin, their blood culture at the time of colonization was negative but repeat blood culture was positive.

All of the 6 infants had thrombocytopenia (mean 162 & median 122) and higher immature/ total neutrophil ratio (mean 0.65 & median 0.71). In all of these infants *Pseudomonas* isolates were sensitive to Gentamicin, and they were on appropriate single empiric anti-*Pseudomonal* antibiotic at the time of clinical suspicion. One of the newborns also received intravenous immunoglobulin (IVIg) as an adjunct therapy in view of deteriorating clinical condition.

Discussion

Incidence

Our incidence of culture positive *P. aeruginosa* sepsis is slightly less than data from other developed nations [9,14,15], and significantly less than the previously published data from another Australian study (4.6% vs. 12.5%) [10]. *P. aeruginosa* as a case series has been mainly reported as a part of outbreak [2,5,16,17]. In our review of literature we could find only 3 studies of *Pseudomonas spp* in non-outbreak settings [12,13,18]. Table 2 provides summary of comparison between 3 studies and our series. To the best of our knowledge this is the first Australian series reporting clinical features, laboratory investigations and complications associated with *P. aeruginosa*.

In our series, only 6 out of total 49 of *P. aeruginosa* isolates between 2002-2013 were from blood culture. This gives us a low attack rate of *P. aeruginosa* infection (12.2%). Jefferies et al. in their systematic review of *P. aeruginosa* outbreaks reported attack rate of 22% [11]. Despite the fact that *P. aeruginosa* is associated with low attack rate, our results showed that a third of neonates who were infected had prior colonization followed by blood stream infection. Kadambari et al. reported similar findings and both of these infants died [18]. This raises the question whether prior colonization with *P. aeruginosa* in Extremely Low Birth Weight (ELBW) infant warrants the use of dual anti-p*seudomonal* agents.

Table 1: Shows the clinical characteristics of 6 neonates with *Pseudomonas aeruginosa* sepsis.

Case	Birth weight (Grams)	Sex	Gestational Age (Weeks)	Day of diagnosis (Days)	Clinical Features	Empirical Antibiotic	Rationalized Antibiotic	Inpatient Stay (Days)	Outcome	Morbidity
1	1009	M	30	24	Bradycardia, desaturations and feed intolerance	Vanc, Imi	Vanc, Gent	73	Survived	No complications
2	696	F	24	7	Septic shock	Vanc, Imi	Mero, Gent	165	Survived	BPD, IVH
3	653	M	25	4	Hyperglycemia, Increasing ventilator requirement, Septic Shock	BP, Cefta	Imi, Gent	11	Died	-
4*	840	M	25	12	Septic Shock	Vanc, Imi	IVIG added	12	Died	-
5*	597	M	23	5	Septic Shock, DIC, Renal Failure	BP, Gent, Fluclox	Vanc, Imi, Fluclox	7	Died	-
6	1096	F	26	6	Septic Shock, DIC, Renal Failure	Vanc, Imi	Mero, Cipro	112	Survived	BPD, IVH

*Prior colonization with *Pseudomonas aeruginosa*.

Vanc: Vancomycin, Imi: Imipenem, Gent: Gentamicin, Mero: Meropenem, BP: Benzylpenicillin, Flucox: Flucloxacillin, Cipro: Ciprofloxacin, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular Hemorrhage

Table 2: Shows comparison between *Pseudomonas Aeruginosa* blood stream infection between current data and other similar studies.

Location	Australia	Turkey	United Kingdom	United States
Study period (years)	2002-2013 (11 years)	2006-2010 (5 years)	2005-2011 (7 years)	1989-1993 (5 years)
Type of study	Retrospective	Retrospective	Retrospective	Retrospective case control
Study population	Neonates admitted in NICU	-Same-	-Same-	-Same-
Total number with Blood stream infection with *Pseudomonas aeruginosa*	6	9	39	22
Mean gestation	25.5	31	26	27.4 ± 0.4
Mean weight (grams)	815.16	1515	840	911± 48
Sex ratio (M:F)	4:2	6:3	1:3	15:7
Mean time of onset of infection (days)	9.6 (4-24)	(5-41)	14 (1-262)	44 ± 10 (6-192)
Clinical features	Episodes of Brady and desaturation, Feed intolerance.		Hyperglycemia a week before positive culture, increasing oxygen requirements, Temperature instability, bradycardia	Feeding intolerance, worsening respiratory distress, Increase apnea and bradycardia, temperature instability.
Mortality	3/6 (50%)	3/9 (33.3%)	15/39 (38.5%)	11/22 (50%)
Complications	Shock, DIC		Not stated	NEC

DIC: Disseminated Intravascular Coagulopathy, NEC: Necrotizing Enterocolitis

Our data presented a seasonal trend; all infected cases were recorded between the months of April-June, and most isolates (83%) were from the warmer months (January-June). In adult studies, increase in gram-negative infection rates has been reported during summer months [19,20]. Eber et al. postulated that the increase in temperature not only increases the bacterial growth and hence colonization but also increases its virulence [19]. This may explain the higher prevalence of gram-negative infections in neonates in warmer countries [21,22]. Furthermore, this is the first study in English literature reporting seasonal variations in *P. aeruginosa* colonization and blood stream infection in neonates. This needs validation with a larger study with prospective epidemiological surveillance. If proven true, this particular observation has important implication in infection control as increased surveillance during warmer months may reduce rate of blood stream infection.

Clinical profile and risk factors

While there has been reports of *P. aeruginosa* contributing to Early Onset Sepsis (EOS) [21,22] it rarely is a cause of EOS in developed countries [23,24]. We could not identify any clinical features or laboratory investigations that could help us differentiate *P. aeruginosa* sepsis from infections caused by other gram-negative organism. This is consistent with the current literature from developed countries [12,18,25]. In contrast to the findings reported by Leigh et al., we did not find higher rate of Necrotizing Enterocolitis (NEC) in the infected neonates. Leigh et al. suggested that the risk factors associated with developing *Pseudomonas* sepsis include a longer ventilation, prolonged antibiotics use and total parenteral nutrition (TPN) and duration of hospital stay. However many of our patients were diagnosed with the infection within a median age of 6.5 days. This is similar to the series reported by Erol et al., while Leigh et al. reported a later onset (44 ± 10 days) [12,13]. Furthermore ELGANs inevitably require prolonged ventilation, TPN and perhaps antibiotics use due to the nature of their condition. The study by Erol et al. has a shorter requirement of ventilation and duration of hospital stay because those infants were more mature [13]. Kadambari et al. reported that mortality was also associated with abdominal distension [18]. We could only conclude that ELGANs and ELBW are risk factors to developing the *Pseudomonas* sepsis.

Mortality

Half of the infected neonates died. This result is similar to Leigh et al. whereby mortality rate decreases exponentially as the infant matures. These findings are consistent with Erol et al. who reported a lower mortality rate (33%) in a more mature infant population [12,13]. Though incidence of *P. aeruginosa* greatly varies geographically, it is universally reported as a fatal organism with most of the studies around the world reporting mortality up to 50%-100% [15,26,27].

Choice of antibiotics

All isolates were sensitive to Gentamicin and this trend did not change in the span of 12 years. Leigh et al. in their data collected from 1989 to 1993 reported 19 out of 22 pseudomonas isolates were sensitive to Gentamicin. Erol et al. in their recent publication reported all 9 isolates of *P. aeruginosa* sensitive to Ciprofloxacillin, 7 to gentamicin and Imipenem, 1 to Ceftriaxone and 6 to Ceftazidime. While Kadambari et al. reported a single gentamicin-resistant isolate associated with neonatal death. Antibiotic resistance of *P. aeruginosa* is attributed to its characteristic cellular architecture, versatility and larger size of *P. aeruginosa* genome, and a probable plasmid mediated antibiotic resistance. Reports of increasing resistance of *P. aeruginosa* to common antimicrobials have been published from around the world [28,29]. Even though there has not been a changed in sensitivity, the mortality and morbidity rate remains high.

The main limitation in our study is sample size. It is difficult to make any firm conclusions from our data. We could only hypothesize the potential benefits in the choice of antibiotic therapy. Based on our study, we suspect that there may be a role for dual anti-pseudomonal therapy in patients who are previously colonized with *P. aeruginosa*.

Conclusions

In developed countries, *P. aeruginosa* is a relatively uncommon cause of LOS in newborns, but is associated with high mortality rate. It seems to follow a seasonal trend in our series. Clinical features and routine laboratory investigations do not help to differentiate this deadly organism from other gram-negative bacteria. Apart from low immunity there are no additional specific risk factors, which can lead to this infection. There may be a role for dual anti-pseudomonal agents in ELGANs especially those who have been previously colonized.

Acknowledgements

Ms Kaye Bawden, Data Manager, Monash Newborn and Ms Despina Kotsanas, Senior Scientist, Infectious Diseases Department, Monash Health.

Contributors' Statements

Efrant Harnaen: Dr. Harnaen conceptualized and designed the study, collected data and drafted the initial manuscript.

Tejas Doctor: Dr. Doctor helped in data collection, carried out the initial analyses, reviewed and revised the manuscript.

Atul Malhotra: Dr. Malhotra designed the data collection, coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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