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A MULTIDRUG RESISTANT *PSEUDOMONAS AERUGINOSA* OUTBREAK IN NEONATAL INTENSIVE CARE UNIT OF PHILIPPINE GENERAL HOSPITAL

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ABSTRACT

Background: For the past 3 years, the Neonatal Intensive Care Unit (NICU) of UP-PGH had *Enterobacter, Klebsiella* and Candida as the top hospital-acquired isolates. *Pseudomonas aeruginosa* isolates are usually low in occurrence or in a mixed culture with other organisms, and are considered contaminants. The occurrence of several fatal *Pseudomonas aeruginosa* infection in the NICU reported in June 2001 exhibiting antibiotypes resistant to all potentially active antibiotics warranted this investigation and interventional measures.

Patients And Methods: Upon notification of the cases, an interventional investigation was conducted. All cases with isolate of *Pseudomonas aeruginosa* were cohorted. Specimens of all babies admitted to the NICU 3B area were sent to the laboratory for surveillance culture. Once *Pseudomonas aeruginosa* was isolated from a patient, the patient was transferred to the cohort area until the demise or discharge. During the outbreak period the following interventions were performed: 1.) Training of entire health care team on Infection Control and Prevention. 2.) Recommendations on antibiotic regimens depending on the sensitivity pattern of the isolates. 3.) Environmental cultures with changes in the use of disinfectants. 4.) Closing the NICU for general cleaning.

Results: 39 cases were reviewed for the duration of the outbreak from June 1- Sept. 30,2001. All cases except 1 were admitted to NICU 3B area because of prematurity (72%). Underlying diseases noted were sepsis(26%),severe asphyxia (13%),meconium aspiration, multiple congenital anomalies, Hyaline Membrane Disease and PDA (10%). The most common clinical manifestations seen at least 24 hours prior to isolation of *Pseudomonas aeruginosa* were bleeding (33%) jaundice (20%) and respiratory distress/ hypoxia (17/32) for mechanically ventilated babies. All cases with ocular involvement presented with eye discharge. Risk factors identified were endotracheal intubation (82%) and by umbilical catheterization(62%). Twenty five out of 39 cases died with a case fatality rate of 64%. 96% of the *Pseudomonas aeruginosa* isolates were resistant to Ceftriaxone, Imipenem, and Meropenem, 88% to Piperacillin-Tazobactam and 46% intermediate, 17% resistant to Ceftazidime. Ciprofloxacin is the only drug with the highest in vitro sensitivity pattern of 75%. Environmental cultures showed isolation of the same strains from sinks and left-hand fingers of a nurse-on-duty at the NICU 3B area.

Conclusion: It is believed that control of the outbreak was achieved through cohorting, educational measures, regular thorough cleaning of the sinks, use of effective disinfectants, appropriate use of antimicrobials and hand washing.

INTRODUCTION

Nosocomial infections in neonatal intensive care units (NICU) are associated with increased mortality rates, prolonged duration of hospitalization in survivors and increased cost of neonatal health care. In contrast to the relatively low incidence of infections in well baby nurseries, the incidence of hospital – acquired infections in NICUs is often high[1,11]. The frequent exposure of critically ill neonates in NICUs to invasive devices and procedures further increases the risk of infection.

The microorganisms that cause nursery acquired infections are diverse and may include bacteria, fungi and viruses and virtually all human pathogens and commensal organisms. In the high risk nursery, the spectrum of infection is broader and organisms not normally pathogenic in healthy newborns may be seen.

The emergence of multi drug resistant organisms has changed the etiology of nosocomial infection over the years, most likely related to the use of newer broad spectrum antimicrobials. Nosocomial gram-negative enteric pathogens like *Pseudomonas* and *Enterobacteriacae* causing epidemics or outbreaks are often resistant to multiple antibiotics and have been a progressive, persistent problem in most NICUs today.

Pseudomonas aeruginosa, like many other non-fermenting gram-negative rods, is a saprophytic organism widespread in nature, particularly in moist environments (water, soil, plants and sewage) and endowed with only weak pathogenic potential. However, because of its ability to survive on inert materials, minimal nutritional requirements , its tolerance of a wide variety of physical

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conditions including temperature, its resistance to most antiseptics and antibiotics, it has become an opportunistic and frequent nosocomial pathogen[1].

Moisture is a critical factor in hospital reservoirs of *Pseudomonas aeruginosa*.In hospitals, sinks, nebulizers, humidifiers, antiseptics, tubings, and other equipments can act as reservoirs of *Pseudomonas aeruginosa*[2,3].

In most cases, the disease process begins with alteration or disruption in the integrity of physical barriers, such as the skin and mucous membranes, or circumvention of normal host defenses, as with intravenous lines, urinary catheters or endotracheal tubes.

Pseudomonas aeruginosa may be responsible for a wide range of hospital –acquired infections such as pneumonia, bacteremia, urinary tract infection, and other organ system involvement. Several *Pseudomonas aeruginosa* outbreaks usually in intensive care units involving patients with impaired defense systems or who have undergone invasive procedures and surgery have been reported [4,5]. They particularly tend to suffer from severe and fatal *Pseudomonas aeruginosa* infection.

At the Neonatal Intensive Care Unit of UP-PGH, *Pseudomonas aeruginosa* isolates are usually low in occurrence or are in mixed culture with other organisms and are considered contaminants. The occurrence of several fatal multidrug-resistant *Pseudomonas aeruginosa* infections in the NICU warranted this interventional investigation.

OBJECTIVES:

It is therefore the aim of this epidemiologic investigation includes the following:

1 To characterize the patients colonized and infected by *Pseudomonas aeruginosa* during the outbreak period from June 1, 2001 to Sept. 30,2001 at the Neonatal Intensive Care Unit of UP-PGH.
2. To determine the factors that may have caused the unusual increase in the number of cases.
3. To institute and evaluate the control measures implemented during the outbreak.

PATIENTS AND METHODS

Case Definition

A case was defined as any infant admitted at NICU diagnosed to have nosocomial infection with an isolate of *P. aeruginosa* from June 1 , 2001 to Sept. 30,2001.

Determination of an Outbreak

From 1998 to 2001, *Enterobacter, Klebsiella and Candida* were the top nosocomial isolates in the NICU. The increased number of *Pseudomonas aeruginosa* isolates for the year 2001 (Fig 1) has confirmed the presence of an outbreak which started in June 2001. Afterwhich, measures to control spread of infection were instituted.

Epidemiological Investigation

Setting

The main neonatal intensive care unit consists of 60 beds , measures 306 square meters and is divided into 3 areas. NICU 2 is for babies completing medications (transitional unit) , NICU 3A for intermediate care, and NICU 3B for mechanically ventilated or critically-ill babies. Curtain dividers are used with variable number of beds assigned to each area depending on the number of babies that can be accommodated. A smaller neonatal unit (NICU 1), located opposite the main neonatal unit, is for well baby deliveries with a capacity of 20 beds. Both nurseries are single room, without separate cubicles and located on the 4th floor of a tertiary teaching hospital which serves as a referral center for high- risk pregnancies. Admission to the high risk nursery (NICU 2 , 3A, 3B) average 350 babies per month or 15 babies per day.

The standard empiric antibiotic regimen for patients suspected to have sepsis used in the neonatal unit for the past 3 years were as follows:

a. Newborns weighing less than 1500grams
   Imipenem/Meropenem 40- 60 mg/kg/day in 2 divided doses
   Aminoglycoside (Amikacin) 15 mg/kg/day in 2 divided doses
b. Newborns weighing more than 1500 grams
   Piperacillin-Tazobactam at 120 mg/kg/day in 2 divided doses
   Aminoglycoside (Amikacin) 15 mg/kg/day in 2 divided doses

The antibiotic regimen was replaced according to the sensitivity patterns of the isolated microorganism.

On June 2001, a noted rise in the number of nosocomially acquired *Pseudomonas aeruginosa* isolates were reportedly seen in the main nursery. The patients were then cohorted and were assigned an area. A separate nurse was assigned to all those affected and a specific sink near the cohort area was assigned for use only by those handling the infected patients. A physical barrier (curtain) was used to divide the main nursery into those cases with

During the outbreak investigation, blood, stool and endotracheal aspirate (if feasible) were sent to the laboratory for culture and sensitivity testing of all babies at NICU 3B. Once *Pseudomonas aeruginosa* was isolated from a patient, the patient was transferred to the cohort area until the demise or discharge.

Description of Cases

The following information were collected from the patients:

a) Demographics- name, case number, age, sex, gestational age, location, duration of stay at the NICU
b) Clinical Data- date of onset of signs and symptoms, and laboratory findings
c) Risk factors- birth weight, underlying diseases, invasive procedures done, antimicrobial therapy and other underlying medical conditions.

On July 24, 2001, the main nursery was closed for general cleaning. All cases were transferred to an 8 bed capacity room adjacent to the main nursery. All new admissions were admitted in the small neonatal unit. Admissions were limited to high risk deliveries only. Interventional measures were conducted from July 25,2001 through Sept. 30,2001. Stools were cultured upon admission and when infection was suspected. Blood and specimens from other sites were cultured as deemed necessary.

During that period, the following interventions were performed:

a) Training of the entire health care team (nurses, nursing assistants and physicians) to avoid cross-contamination , with emphasis an hand washing and contact precautions.
b) Revision of Recommendations on the standard empiric antibiotic regimen to:

Ceftazidime 100 mg/kg/day in 2 divided doses and Aminoglycoside (Amikacin) 15 mg/kg/day in 2 divided doses Once multi drug resistant *Pseudomonas aeruginosa* is isolated, antibiotics were shifted to Ciprofloxacin at 20 mg/kg/day in 2 divided doses.

Multidrug resistant *Pseudomonas aeruginosa* is defined as an isolate resistant to at least Aminoglycosides, 3rd/4th generation Cephalosporins and Carbapenems. Antibiotic susceptibility was determined for all isolates by standard agar diffusion method. MICs were determined by a standard agar dilution method and interpreted according to national guidelines.

c) Environmental cultures

During the outbreak, several environmental cultures were done . The first was obtained during the investigation prior to closing the nursery for general cleaning dated July 16, 2001. The second was done 2 weeks later before the opening of the main nursery dated July 31,2001. The 3rd was done when the decontaminating agents used was just Lysol 6% and the fourth was done after the use of 3 kinds of decontaminating agents namely Lysol 6%, Benzoyl 3% and Para- Acetic Acid 10%.

On August 9, 2001, the main nursery was opened, but all remaining colonized and infected babies remained in the cohort room until their demise or discharge

RESULTS

Background Rates

For the past 3 years, the top 3 isolates for nosocomial infection at PGH NICU were *Enterobacter, Klebsiella and Candida*. *Pseudomonas aeruginosa* isolates have an average incidence of 1-3 isolates (0.01-0.03%) per month from Jan.- May 2001 (Fig 1). In June 2001, a total of 21 (43%) *Pseudomonas aeruginosa* isolates were reported from a total of 49 nosocomial isolates in NICU. Of the babies affected, 13 came from NICU 3B, 12 of whom died and only 1 survived and was

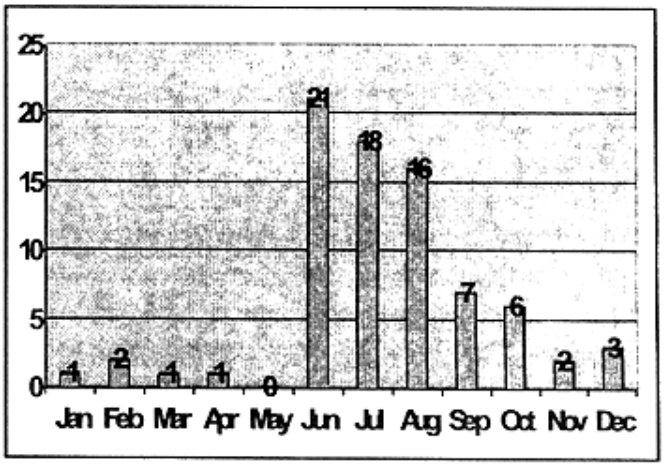

Fig 1. Pseudomonas aeruginosa Isolates at UP-PGH Neonatal Intensive Care Unit Year 2001

discharged. This is twenty times higher than the average incidence of *Pseudomonas aeruginosa* isolate and infection for the past 3 years, thus establishing an outbreak.

Control Measures

Basic control measures especially hand washing, was intensified and regular cleaning of the sinks every

4 hours were implemented. Isolation and cohorting of babies by location and by staff was strictly implemented. A policy on Guidelines for Admission at the NICU of PGH was drafted by PIDS, Nursery Section , OB Section and the Adhoc Committee of PGH and was circulated and implemented in order to prevent unnecessary overcrowding and implementation of regular cleaning of NICU.

Case Characteristics

A total of 39 cases were reviewed for the duration of the outbreak. All cases were admitted at NICU 3B, with the exception of one that was from NICU 3A . All the 12 cases from the month of June were identified only after their death 2' to disseminated intravascular coagulopathy (DIC) 2 to sepsis but 1 survived because of ocular involvement only. Cohorting was started on July 3 after the PIDS section was notified of the outbreak. Another 15 cases were then seen , 10 (66%) of whom died and only 5 (33%) survived before the main nursery was closed on July 24th. All cases were transferred to the cohort room. Only 2 new cases were seen coming from NICU 1 room where the critically-ill babies were admitted for the 2 weeks the main nursery was closed for cleaning. On Aug. 9th, the main nursery was re-opened and 9 more new cases were reported from NICU 3B area but the sensitivity pattern of P. aeruginosa isolates were improving with only 1 death attributed to Pseudomonas infection. The investigation was thus terminated on Sept. 30,2001.

Clinical Profile of the Cases

Majority of the cases were preterm (72%) with a mean pediatric aging of 33.5 weeks and mean birth weight of 1.642 kgs with 22 (56%) of the babies weighing below 1.5 kgs. A male to female ratio of 1:1.4 and almost equal distribution of small for gestational age SGA (49%) and appropriate for gestational age AGA (51%) were seen. The babies were admitted to NICU3B for sepsis (26%), severe asphyxia (13%), Hyaline Membrane Disease Meconium Aspiration (10%), Patent Ductus Arteriosus (10%), and Multiple Congenital Anomalies (10%). (Fig 2.).

Fig 2. Underlying Diseases of Cases Admitted to NICU 3B of UP-PGH, June- Sept. 2001

Underlying Diseases	No. of Cases (%)
Sepsis	10 (26%)
Severe Asphyxia	5 (13%)
Hyaline Membrane Disease	5 (13%)
Meconium Aspiration Syndrome	4 (10%)
Multiple Congenital Anomalies	4 (10%)
Patent Ductus Arteriosus	4 (10%)
Pneumonia	3 (7%)
IUGR	2 (5%)
Transient Tachypnea of Newborn	2 (5%)

The most common clinical manifestations seen at least 24 hours prior to the isolation of the organism were bleeding (33%) and jaundice (20 %) followed by anemia (13%) which may be secondary to bleeding.

Fig 3. Presenting Signs and Symptoms of Cases Prior to Isolation of P. aeruginosa

Signs and Symptoms	No. of Cases (%)
Bleeding (Endotracheal, OGT, Petecchiae, Purpura)	13 (33%)
Respiratory Distress/Desaturation	14 (36%)
Jaundice	8 (20%)
Anemia	5 (13%)
Sclerema	3 (8%)
Eye Discharge	3 (8%)
Bloody stools	2 (5%)
Vomiting	1 (2%)
Seizures	1 (2%)
Wound Discharge	1 (2%)

Respiratory distress or desaturation 17/32 (53%) was the most common manifestation for intubated patients. All cases with ocular involvement presented with eye discharge. A case with omphalocoele had wound discharge where the organism was isolated (Fig 3.).

Risk Factors

Endotracheal intubation (82%) was the most common invasive procedure done on the cases followed by umbilical catheterization (62%) usually done within 24 hours after birth. Partial exchange transfusion was done in 10 cases (26%) for intractable sepsis where the organisms were isolated from the blood (Fig 4).

Fig 4. Invasive Procedures Done Prior to Isolation of Pseudomonas aeruginosa.

Invasive Procedures	No. of Cases (%)
Intubation	32 (82%)
Exchange Transfusion	10 (26%)
Umbilical Catheterization	24 (62%)
Partial Parenteral Nutrition	2 (5%)
Cutdown	1 (3%)
CPAP	1 (3%)
Urinary Catheterization	1 (3%)

Outcome

Twenty five out of 39 cases died with a case fatality rate of 64%. Twelve cases died of DIC secondary to *Pseudomonas sepsis* on the 1st month of the outbreak

to *Pseudomonas sepsis* on the 1st month of the outbreak with mean hospital stay of 6.5 days only. All the babies were admitted to NICU 3B for prematurity (11/12) were mechanically ventilated and were empirically stated on Meropenem/Imipenem or Piperacillin-Tazobactam depending on their birth weight and Amikacin. The only survivor is the case with eye involvement only. Six more fatalities followed with *Pseudomonas sepsis* as the cause of death even after the strict implementation of infection control guidelines. The remaining 8 deaths were due to other causes and were seen during the last months of the outbreak period.

Microbiological Investigation

During the outbreak period, the *Pseudomonas aeruginosa* isolates were noted to be evolving to multi resistant strains. Blood isolates showed resistance to commonly used anti-pseudomonal drugs in the hospital. 96% of the *Pseudomonas aeruginosa* isolate were resistant to Ceftriaxone, Meropenem, and Imipenem, 88% for Piperacillin-Tazobactam and 46% had intermediate sensitivity to Ceftazidime and 17% resistant to Ceftazidime. Ciprofloxacin is the only drug with good in vitro sensitivity pattern of 75% (Fig 5). The same patterns were seen in the endotracheal tube aspirate and eye discharge *Pseudomonas aeruginosa* isolates .

Flg 5 . In vitro Antibiotic sensitivity pattern of Pseudomonas Aeruginosa isolates in Neonatal Intensive Care Unit of Philippine General Hospital Blood Specimens June- Sept, 2001

ANTIBIOTIC (AB)	TOTAL # OF ISOLATES TESTED (TNI)	SENSITIVE (%)	INTERMEDIATE (%)	RESIS-TANT (%)
1. Aztreonam	19	1 (5%)	2 (10%)	16 (85%)
2. Amikacin	10	4 (40%)	2 (20%)	4 (40%)
3. Netilmicin	29	7 (24%)	2 (7%)	20 (69%)
4 Ciprofloxacin	12	9 (75%)	1 (8%)	2 (17%)
5. Ceftazidime	35	13 (37%)	16 (46%)	6 (17%)
6. Ceftriaxone	27	0 (0%)	1 (4%)	26(96%)
7. Cefepime	22	5 (23%)	10 (45%)	7 (32%)
8. Cefpirome	7	0 (0%)	1 (14%)	6 (86%)
9. Piperacillin-Tazobactam	25	3 (12%)	0 (0%)	22 (88%)
10. Imipenem	26	1 (4%)	0 (0%)	25 (96%)
11. Meropenem	27	1 (4%)	0 (0%)	26 (96%)
12. Gentamicin	3	1 (33%)	0 (0%)	2 (67%)

Twenty five (64%) of the cases who were given the initial empiric treatment (Meropenem/ Imipenem and Piperacillin-Tazobactam) were shifted to Ciprofloxacin (28%), Meropenem (28%), Cefepime (20%) and Ceftazidime (16%). The cases whose antibiotics were shifted to Meropenem were initially given Piperacillin and 4 out of 5 were again changed to Ciprofloxacin and the other to Cefepime. Three cases were given Amphotericin B because of concomitant *Candida* isolate for which 2 of them eventually died of *Candida* infection.

Environmental Cultures

Initial environmental cultures done July 16, 2001 by the Infection Control Committee showed isolation of *Pseudomonas aeruginosa* from sink # 1 and #2 located at NICU 3B area and from the hands of a physician in charge of NICU3B babies, all of which had the same antimicrobial susceptibility. A multidrug resistant *Pseudomonas aeruginosa* isolate was seen from the left hand fingers of a nurse-on –duty in charge of NICU 3B babies after handwashing. Subsequent environmental cultures even after cleaning of the NICU showed persistent growth of multidrug resistant *P. aeruginosa* from the sinks and faucet of the main NICU until the use of 3 disinfectants showed reversion of resistance of the isolates to the antimicrobials.

DISCUSSION

Nursery outbreak of *Pseudomonas aeruginosa* infection has been associated with environmental contamination, respiratory therapy equipments, suction machines and disinfectants[2,3,6]. It is likely related to breakdown in infection control techniques such as overcrowding, understaffing and other major disruptions of nursery routine[7]. These were the same reasons observed in the NICU of UP-PGH. Being a tertiary hospital, overcrowding and understaffing remain to be perennial problem. The route by which the epidemic strain was introduced to the unit cannot be traced since the first patients died rapidly and the growth of *Pseudomonas aeruginosa* were all post mortem. However, secondary dissemination within the unit remained limited to the area where the critically-ill , mechanically ventilated patients were the ones infected. The presence of *Pseudomonas aeruginosa* in the environmental culture and in the hands of health care workers with the same antibiograms as with the isolates from the patients suggest that the spread was related to cross- contamination between patients and via the hands of the health care workers, although further typing analysis of *Pseudomonas aeruginosa* isolates to differentiate the outbreak from unrelated isolates was not done.

Several risk factors have been associated with the development of nosocomial infection in newborns, such as low birth weight, underlying diseases, type and

duration of invasive procedures and colonization during the hospital stay[7,8]. Most of our cases were mechanically ventilated and umbilical catheterization was done requiring frequent handling and suctioning , these increasing their risk for acquiring a nosocomial infection. Signs and symptoms of bleeding and jaundice were the indicators of severe *Pseudomonas* sepsis and may be fatal. Respiratory distress or hypoxemia suggests acquiring nosocomial infection through the respiratory tract progressing to bacteremia particularly in mechanically ventilated patients.

The use of antibiotics particularly cephalosporins has been associated with a greater risk of colonization and infection with multiresistant bacteria, both in experimental models and clinical trials[6,9]. Nosocomial infections in this unit for the past 3 years has been treated with Carbapenems and Amikacin due to predominantly gram-negative isolates this poses a great risk for developing multiresistant bacteria.

When the outbreak was confirmed, the Neonatology, Pediatric Infectious Disease and OB services together with the Infection Control Committee of the hospital had several meetings . Problems were identified and the following measures and recommendations were drafted and implemented:

1. Guidelines for Limiting Admissions in NICU UP-PGH
2. Thorough hand washing of all personnel entering and handling patients at the NICU
3. Use of Sterile water for humidifiers
4. Cleaning and disinfecting the sinks using Lysol 6% followed by Para –acetic acid 10% every 2-3 hours.
5. Regular general cleaning of NICU every 3 months
6. Regular workshop on Infection Control Measures and Procedures for all personnel including doctors, students, nurses and nursing aids at the NICU are conducted.

CONCLUSION

It is believed that control of the outbreak was achieved through cohort nursing, educational measures to prevent cross- contamination, regular thorough cleaning of sinks, regular use of effective disinfectants, appropriate use of antimicrobials and hand washing.

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