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PSEUDOMONAS INFECTIONS IN HOSPITALIZED INFANTS AND CHILDREN METRO MANILA 1984

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ABSTRACT

In 1984 out of 6,270 total pediatric admissions at Lungsod ng Kabataan (LnK) Children's Hospital, Metro Manila, 171 had positive cultures for Pseudomonas *aeruginosa* with neonates as the most commonly affected. Symptomatology and blood counts were not significant enough to be considered diagnostic. Positive cultures from specimens, particularly the blood, was the only finding that clinched the diagnosis, just as it was 10 years ago in a study at the Philippine General Hospital.

Sensitivity tests showed changes from previous reports; to some extent this may have been due to a difference in presently available antibiotics. As mortality is still high and the diagnosis still complicated and costly, time-tested simple preventive measures are important.

Introduction

Infections caused by the ubiquitous Pseudomonas especially the opportunistic pathogenic to man, *Pseudomonas aeruginosa,* are not in the top morbidity and mortality lists anywhere. Yet these continue to be considered dreadful diseases which cause considerable concern in hospitals and to those deeply concerned with the health of children.

It is known that the disease commonly affects neonates particularly the debilitated or critically ill, who need nasogastric tubes, suction and humidifying apparatus or assisted ventilation. It is also often observed among malnourished children or those who have chronic illness requiring prolonged antibiotics or immuno-suppressive treatments. The organisms thrive well under suitable conditions, particularly moist or wet environments. Although these organisms are said to be present in the gastrointestinal tract of normal persons, they may cause harm under unfavorable conditions.

Furthermore for specific treatment, Pseudomonas requires expensive antibiotics which have to be administered continuously for long periods, but still may result in unnecessary deaths under the circumstances described. It is a problematic organism and is not as innocuous as it was thought to be. Therefore it can drain the family budget and cause much anxiety.

In the Philippines reports on Pseudomonas infections, are few and far between. The incidence may appear significant but unfavorable predisposing factors such as malnutrition and prematurity cause high mortality. Pseudomonas infection is commonly associated with burns and chronic wounds which adversely affect prognosis and outcome. Abroad much has been written on this dreadful complication of burns but locally only the UP-PGH* group has been vocal about this dread.

Besides seeking ways of preventing Pseudomonas infection, its course and antibiotic response are emphasized for follow-up studies to improve outcome and reduce health costs.

In this study, out of 6,720 admissions for 1984, 171 cases gave positive cultures for *Pseudomonas aeruginosa*. This number is quite high the reasons for which are presented in the paper as well as changes in the pattern and outcome of the infection.

Objectives

General:

To determine current trends and pattern of Pseudomonas infections.

Specific:

- To seek sources of infection with Pseudomonas as well as contributing factors.
- To determine manifestations which will serve as clues to infection with Pseudomonas.
- To seek ways of expediting diagnosis of Pseudomonas infection.
- To determine changes in the progress and outcome of Pseudomonas infections.
- To seek simple and inexpensive procedures in their management.
- To determine sensitivity pattern of the organism to currently available or commonly prescribed antibiotics.
- To recommend preventive measures.

Materials and Methods

All patients admitted to the wards or in the Intensive Care Unit if positive for Pseudomonas in cultures, would be diagnosed as Pseudomonas infection plus the underlying disease (if any) and managed accordingly.

The sources of specimens for cultures are enumerated in Table 7. There may be more than one site of culture.

A brief description of the technic of culture and biochemical identification of Pseudomonas is as follows: Specimens are streaked on blood agar and McConKey

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plates, incubated for 24 hours at 37°C after which the plates are read and biochemical tests are performed. If Pseudomonas is suspected, the Sellers test is added and another 24 hours incubation is required.

All Pseudomonas positive cultures are reported and the corresponding patients became the subjects of this study, with a total of 171.

Sensitivity tests were done as shown in Table 8. Treatments were given depending on the organisms, sensitivity test and condition of the patients.

To test for a possible source of infection, sterile water contained in bottles used for suctioning was cultured on different occasions. A total of 9 samples were obtained from three bottles upon opening, then two hours and 6 hours after exposure. Results were consistent. The six specimens obtained at 0 and 2 hours did not grow anything on culture. The three specimens obtained at 6 hours all grew Pseudomonas.

Postmortem examinations were possible only in 15 cases and expected or usual characteristics were sought.

Results and Discussion

In 1984 out of 6,720 pediatric admissions in *LnK Children's Hospital, a total of 171 patients had positive cultures for *P. aeruginosa.* This is a high incidence compared to a 10-year retrospective review locally (1956-1965), which gave 38 positive cases.

Distribution of cases by age and sex

The highest incidence of Pseudomonas infection is in the neonate and infant (2 mo. to 2 years) and correspondingly also had the highest mortality (Table 1). This was followed by the 2-4 year-old children (34.8%).

Table 1. Distribution of Pseudomonas infections by age and mortality

Age	*Number of Patients*	*Mortality*
0 - 1 month	57 (33.3%)	21 (36.8%)
2 mos. - 2 yrs.	74 (43.3%)	37 (50.0%)
2 - 4 years	23 (13.4%)	8 (34.8%)
5 - 9 years	10 (5.9%)	0
10 - 14 years	7 (4.1%)	1 (14.3%)
Total	171	67 (39.0%)

The age distribution of children who had positive blood cultures is shown in Table 2 with corresponding deaths. It is evident that the neonate and infant with Pseudomonas septicemia constitutes critical age period.

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Table 2. Age distribution with positive blood cultures for Pseudomonas and their corresponding mortality

Age	*Total*	*Died*	*Percent*
0 - 1 mo.	11	7	63.6
2 mos. - 2 yrs.	9	5	55.6
2 - 4 years	2	2	100
5 - 9 years	0	0	0
10 - 14 years	1	0	0
Total	23	14	(61%)

Of 171 patients admitted and diagnosed to have Pseudomonas infections by culture, 65% were males and 35% were females and the corresponding mortality were 40% and 36% (Table 3). These figures may represent a higher incidence among males, but statistical analysis did not show that sex is a significant factor in the occurrence or even in the death of the patients.

Table 3. Pseudomonas infections by sex with corresponding mortality

Sex	*Number of Patients*	*Mortality*
Male	111 (65%)	45 (40%)
Female	60 (35%)	22 (36%)
Total	171	67 (39%)

Pseudomonas patients by hospital classification

In this study, the Intensive Care Unit seemed to be a common site of Pseudomonas infections with a higher mortality than in ward patients (Table 4). This would probably be expected as the patients are usually critical and require different apparatuses.

Table 4. Pseudomonas infections by hospital bed classification and corresponding mortality

Section	*No. of Patients*	*Mortality*
Ward	87 (50.9%)	29 (33.3%)
ICU	84 (49.1%)	38 (45.2%)

A high incidence of Pseudomonas infections among hospitalized patients was noted in certain situations listed in Table 5. These may confirm observations that Pseudomonas flourishes with the use of apparatuses.

Table 5. Possible contributing factors to Pseudomonas infections among hospitalized patients

1.	Acquired post-operatively (post-op wound infections, post-skin grafting, wound discharges)	– 21 (12.3%)
2.	Acquired while on assisted ventilation	– 74 (43.3%)
3.	Malnutrition present	– 35 (20.5%)

Underlying or working diagnosis

The working diagnosis of patients who were subsequently worked up and were found to be positive for Pseudomonas is shown in Table 6. It was not definitely determined that Pseudomonas was contributory to or the main etiologic agent of the illness. As would be expected, the symptomatology was dependent on the underlying disease or the site of the infection.

Table 6. Working diagnosis of patients with Pseudomonas infection and corresponding mortality

Working Diagnosis	*No. of Patients*	*Deaths*
Bronchopneumonia	35	17
Sepsis neonatorum	34	13
Measles and post-measles pneumonia	20	12
Prematurity/RDS	10	2
Urinary Tract Infection	7	0
Meningitis	6	3
Infectious diarrhea	5	1

Manifestations of Pseudomonas infection

The symptomatology presented by the patients were nonspecific and tended to vary with the underlying illness such as pneumonia, measles or diarrhea. This was true even for patients with blood cultures positive for Pseudomonas. As a group, septic neonates presented with poor suck, decreased activity, jaundice and diarrhea, symptoms which are common in sepsis due to other organisms.

The necrotic skin lesions described by Feigin as characteristic were seen in only 2 of the cases in this study. Both were neonates with blackish ulcerations on the upper lip and tongue. There were 21 cases of post-operative wounds and burns which were colonized by Pseudomonas. Fifteen patients had greenish, foul discharge representing the typical purulent discharge of Pseudomonas wound infection.

Of the 4 cases of Pseudomonas meningitis (positive CSF cultures), 3 had an anatomic defect in the form of leaking nasofrontal meningocele. All of them did not grow Pseudomonas on blood culture and the defect was the most probable predisposing factor to the occurrence of meningitis in these patients.

Although there are reports of leukoponia in patients with Pseudomonas infection, no consistent pattern of white blood cell depression or elevation was observed in the present study. The only definite laboratory marker was the growth of the Pseudomonas organism from the sites of culture.

Sites of culture

Cultures were taken from different sites depending on indications (Table 7). A patient could have more than one culture site.

Table 7. Source of Pseudomonas cultures in hospitalized patients

Site	*Number*
Tracheal aspirate	63
Blood	23
Urine	22
Stool	16
Wound discharge	21
Ear discharge	10
Eye discharge	8
Pleural fluid	5
CSF	4
Umbilical discharge	4
Ascitic fluid	2
Lung tap	2
Throat swab	1

Sensitivity tests

The results of the sensitivity tests are shown in Table 8. This was not an exhaustive list as much depended on the availability of discs.

Table 8. Sensitivity patterns by discs diffusion method of Pseudomonas isolates (1983-84)

Antibiotic	*No. of Isolates Tested*	*Sensitive*	*Resistant*
Amikacin	152	129 (84.9%)	23 (15.1%)
Carbenicillin	82	27 (32.9%)	55 (67.1%)
Cefotaxime	82	42 (51.2%)	40 (48.8%)
Gentamicin	56	42 (75.0%)	14 (25.0%)
Tobramycin	132	91 (68.9%)	41 (31.1%)
Netilmicin	83	51 (61.4%)	32 (38.6%)

It appears that in the present study group, *Pseudomonas aeruginosa* was highly sensitive to Amikacin (84.9%), then Gentamicin (75%) and Tobramycin (68.9%).

Antibiotics used for Pseudomonas infection

In the Philippines, between 1956 to 1965, the antibiotics of choice were first penicillin and then chloramphenicol. At that time Colistin was also used with encouraging results.

About one year later the antibiotics that were observed to give favorable results were surbenicillin, colistin and carbenicillin. The following year (1977), the three top choices were amikacin, collatin and sulbenicillin. It is evident that amikacin after 10 years after is quite an effective antibiotic.

Duration of stay of patients

It was observed that 24% of Pseudomonas cases stayed in the hospital for only one week while 22.8% stayed more than a month.

Table 9. Total duration of stay in the hospital

Duration	*No. of Patients*	*Percent*
Less than 1 week	41	24
1 - 2 weeks	28	16.4
2 - 3 weeks	34	19.9
3 - 4 weeks	29	16.9
More than 1 month	39	22.8

Undoubtedly the length of stay did not depend on the antibiotic alone. The general condition of the patient, his previous state of health, age, and social factors could not be disregarded.

Table 10 shows combination of antibiotics that were administered among those who died. The rationale for the combinations was not determined. Perhaps the severity of the illness was what prompted additional antibiotic: perhaps to be "doubly sure" as is often thought.

Table 10. Antibiotic treatment of Pseudomonas infections among patients who died

Antibiotics	*No. of Patients*	*Died*
Ampicillin/Gentamicin	26	11 (42.3%)
Penicillin/Gentamicin	25	7 (28.0%)
Ampicillin/Amikacin	22	9 (40.9%)
Cefotaxime/Amikacin	16	7 (43.8%)
Penicillin/Amikacin	9	4 (44.4%)
One antibiotic only	15	5 (33.3%)

Postmortem reports

Of 67 patients who died, fifteen were autopsied. Results are shown in Table 11. Pseudomonas was cultured postmortem from the post-operative wound discharge in case 1, the pus from the pulmonary cyst in case 13 and the exudate covering the brain in case 15, providing actual proof of Pseudomonas infection. In case 12, there were intestinal ulcerations and evidence of extensive gastroenterocolitis on autopsy. Pseudomonas was cultured from the stool of this malnourished patient while he was alive.

While bronchopneumonia was seen in all 10 cases in which Pseudomonas was cultured from tracheal aspirates, we cannot be certain that it was really the etiologic agent because the organism was not grown from the lesions following autopsy. Neither can we conclude from the gross appearance of the lungs that Pseudomonas was the causative agent.

Summary and Conclusions

In 1984 out of 6,270 total pediatric admissions in a local hospital, 171 had positive cultures for *Pseudomonas aeruginosa*. Specimens were obtained from different sites (blood, CSF, tracheal aspirates and others) depending on indications. Positive Pseudomonas was mostly from tracheal aspirates and the blood.

The age groups most affected were neonates and infants (0-2 years) followed by the 2-4 year group. The sex distribution was not statistically significant.

Although there were the same number of Pseudomonas infections in the wards and the Intensive Care Unit (ICU), mortality was higher in the ICU (45%), than in the former (33%).

Bronchopneumonia and sepsis neonatorum were the most frequent working diagnosis or underlying disease. Significant contributory factors in hospitalized patients were assisted ventilation (43%) and malnutrition (20.5%).

Sensitivity tests gave highest response to Amikacin, Gentamicin, and Tobramycin. This was not an exhaustive list since the tests were dependent or the availability of discs. Antibiotics included are the ones commonly used and available in many localities. By experience less broad antibiotics were not included due to high resistance and only 7 discs were tested at a time.

The patients stayed in the hospital for 1 week to 1 month in almost equal proportions. There were 68 deaths (39%).

Similarly the symptomatology and blood counts were not significant enough to be considered diagnostic. Positive cultures from specimens particularly the blood was the only finding that clinched the diagnosis just as it was 10 years ago.

Changes in antibiotic sensitivity pattern make it worthwhile to do follow-up studies periodically for economic reasons and convenience.

Because the mortality is still high and both diagnosis and management are complicated and costly, time-tested, simple preventive measures such as handwashing, checking and disinfection and cleanliness must be emphasized and practised.

Table 11. Autopsied cases of Pseudomonas infection

	Age	*Sex*	*Working Diagnosis*	*Site of Culture*	*Autopsy Findings*
1.	1 day	M	Pneumonia, S/P jejunal Web Lysis	blood, wound discharge	intestinal adhesions, greenish pus on post-op site, bilateral lung consolidation
2.	1 month	M	Bronchopneumonia, CHD	tracheal aspirate	bilateral lung consolidation, ASD, VSD
3.	1 year	M	Measles bronchopneumonia	tracheal aspirate	extensive bronchopneumonia
4.	2 years	F	Measles bronchopneumonia	tracheal aspirate	extensive bronchopneumonia
5.	5 months	M	Bronchopneumonia, CHD	tracheal aspirate	bilateral lung consolidation, VSD, PDA
6.	1 month	M	Bronchopneumonia, CHD	tracheal aspirate	bilateral lung consolidation, VSD
7.	1 month	F	Diaphragmatic hernia	tracheal aspirate	Bochdalek hernia, hypoplastic left lung, bilateral pleural effusion, intraabdominal bleeding
8.	5 days	F	Sepsis Neonatorum	blood	kernicterus brain, atelectasis of both lungs
9.	7 months	M	Bronchopneumonia, multiple brain abscesses	tracheal aspirate	mild bronchopneumonia, multiple brain abscesses
10.	10 months	M	Post-measles bronchopneumonia	tracheal aspirate	extensive bronchopneumonia
11.	22 days	F	Sepsis Neonatorum	tracheal aspirate	bilateral lung consolidation
12.	9 months	M	Bronchopneumonia, infectious diarrhea, malnutrition	stool	extensive gastroenterocolitis, pneumonias
13.	1 1/2 months	M	Pulmonary cyst, septicemia	blood	infected pulmonary cyst on right lung with greenish-yellow pus rupturing into trachea
14.	3 months	M	Pneumonia, PDA	tracheal aspirate	microabscesses, both lungs, pneumonia on right, PDA
15.	1 month	M	Sepsis, meningitis	blood	bronchopneumonia, gelatinous brain with purulent exudate

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Hilda Lin-Kleiner, Discussant

My discussion will be limited to the following two aspects:

1. Diagnosis of Pseudomonas.

   Pseudomonas is not a fastidious organism. It grows easily, and can be readily recognized by its green-blue color and characteristic fruity well. On blood agar, it also shows a zone of hemolysis surrounding the colony which has an irregular contour. Its biochemical reaction shows that it does not ferment any sugars. In Sellers agars, the slant will be green with a yellow-green fluorescent, thus differentiating it from the Acinetobacters and Alkaligenes.

2. Treatment for Pseudomonas Infection

   2.1 For systemic infections, antibiotics is necessary. The three most commonly used are listed below:

   a. Aminoglycosides:

Gentamicin	+++
Amikacin	+++
Tobramycin	++++
Sisomicin	++
Netilmycin	++

   The most powerful against Pseudomonas is Tobramycin. It is of interest that in this paper, the most sensitive is Amikacin (85%) followed by Gentamicin (75%) then Tobramycin (69%) and Netilmycin (61%) even though we have been using Gentamicin for over 10 years. It must be remembered that these agents are more active in alkaline pH and they may produce oto and nephrotoxicity.

   b. Penicillins:

Carbenicillin (oral)	+
Sulbenicillin	+
Ticarcillin	++
Mezlacillin	++
Azlacillin	+++
Piperacillin	+++

   The last two members are more powerful against Pseudomonas. They are all to be given parenterally except for Carbenicillin. They are all affected by beta-lactomase, and require big doses. For small infants, sodium overload may occur because they are di-sodium salts.

   c. Cephalosporin:

Cefsulodin	++

Ceftazidime	++++
Cefperazone	++
Ceftriaxone	++
Cefotaxime	+
Moxalactam	+

Except for Cefsulodine which is a second generation the rest are all third generation cephalosporin. Ceftazidime is the latest drug that is extremely active against Pseudomonas. It will be available (Fortum by Glaxo) next month. Pseudomonas resistant to all antibiotics are sensitive to this drug.

2.2 For local application:

- 1% silver sulfadiazine (Silvadene, Flammazine) is most useful.
- Providone iodine is effective, but may cause stains.
- Gentamicin should not be used locally due to emergence or resistant of strain.
- Acetic acid – may be effective.

3. Prophylaxis:

We know that one ounce of prevention is better than one pound of treatment. Therefore in order to prevent Pseudomonas complication, the following must be observed –

a. Mechanical scrubbing with soap and water of floor, wall and ceiling.
b. Cleaning of ventilation systems.
c. Autoclave parts of suction and aerosol apparatus.
d. Rinsing aparatus with weak acetic acid.
e. Frequent changing of indwelling catheters, endotracheal tubes, i.v. tubings and needles.
f. U. V. light – In order to be effective has to be on for almost 24 hours.

Bibiano C. Reyes, Discussant

Dr. Fe del Mundo had clearly shown the essentials of diagnosis namely: 1) it is an opportunistic infection or superinfection in patient with some other infection receiving antibiotic, prophylactic or therapeutic or debilitated because of underlying disease, 2) positive cultures confirm the diagnosis.

The clinical findings depend on the site of infection and the patient's underlying disease. Sepsis with this organisms is usually identical clinically to gram (–) sepsis of other organisms. The diagnosis is made by culture. As emphasized, the ubiquitous nature of Pseudomonas enhances its spread. While an unanticipated Pseudomonas infection can occur in any patient, as it is usually hospital acquired, certain population are particularly vulnerable and therefore merit a high index of

suspicion and a low threshold for aggressive intervention when signs of infection exist. There is a long list of relatively uncommon immunocompromised hosts who are rendered unusually susceptible due to congenital or acquired (naturally or iatrogenically), local or generalized impairment of host's defense. In addition to what have been mentioned are the following: neutropenia, hyposplenism, congenital heart disease, malignancies, diabetes mellitus, cystic fibrosis, drug abuse, malnutrition, those who have had prolonged hospitalization with instrumentations, manipulations, indwelling shunts and catheter, respiratory therapy, immunosuppression and other humoral, cellular and compliment immunodeficiencies. Transmission from patient to patient via hospital personnel and equipment is more significant than an airborne spread. Recovery of the organism, however, from the surface of the skin and from the throat, tracheal aspirate or bronchial secretions reflects colonizations and is not necessarily diagnostic of infections. Surfaces of wounds and burns are frequently populated, not necessarily an infection but a prerequisite to sepsis. It can infect almost any tissue or body site, may spread via the hematogenous route, producing septicemia with or without focal lesions in other tissues.

The diagnosis of Pseudomonas infection in the neonate is a sense of urgency, since if untreated, it may rapidly lead to systemic collapse and most likely death, usually identical clinically to other gram negative sepsis and other organism. Once sepsis is suspected, these patients should be managed expeditiously and such should mandate presumptive parenteral therapy until proven otherwise. Diagnostic procedures should be undertaken prior to initiation of presumptive therapy unless the patient presents in extreme, in which case only a blood culture need be obtained. Based on clinical judgement, a septic work-up is decided on, such as culture and sensitivity of blood, CSF, bladder tap urine and aspirates, chest X-ray, antigen-identification, the acute phase reactants, platelet count, and the Band/total neutrophil ratio and total leukocyte count. In neonatal sepsis, the last two are simple tests and can be done within an hour without special laboratory facilities. They are variable aids in the early diagnosis of neonatal sepsis due to their specificity and positive predictive accuracy. The enhanced immunocompetence of older hosts permit individualization based on clinical judgement whether a septic work-up is warranted, and if so, which are indicated.

In general, concern for a toxic child and in most instances, in neonate, prior to the culture results, the use of two antibiotics is warranted and this should include a penicillin (e.g ampicillin or the new cephalosporins) and an aminoglycoside appropriate for the pathogen predictably responsible. Consideration of local sensitivity patterns influence the choice of aminoglycoside when Pseudomonas or other nosocomially acquired gram (–) organism require coverage. In most instances, modifications of specific antibiotic routine or schedule should be determined in the light of C/S reports and clinical development. Antibiotic sensitivity patterns vary from area to area and resistance tends to appear as new drugs are introduced and their use become popular. The impaired defenses as well as the particular epidemio-

logical circumstances of the compromised hosts frequently results in peculiar patterns of bacterial susceptibility that require specific antibiotic therapies.

Neutropenic patients, for example, due to their propensity to infection due to gram ( ) organism, including Pseudomonas, should be treated with broad spectrum antibiotic combination such as carbenicillin, ticarcillin or the new cephalosporins and tobramycin, gentamicin or amikacin. Combinations of gentamicin or other aminoglycoside and carbenicillin or ticarcillin is usually synergistic against many strains of pseudomonas. Use of the two latter drugs alone is associated with the emergence of resistant Pseudomonas and superinfection with resistant Klebsiella during prolonged therapy. Recently an increasing number of strains have been found resistant to gentamicin. Tobramycin or amikacin may be used alone or better in combination with ticarcillin or carbenicillin. Tobramycin and ticarcillin act synergistically in vitro and if given in combination, the emergence of strains resistant to ticarcillin is delayed. At any rate, treatment should be influenced by culture and sensitivity test result. When the clinical picture continue to be supportive of the diagnosis inspite of negative culture results, a presumptive therapy for systemic Pseudomonas infection is a combination of tobramycin or amikacin and ticarcillin or carbenicillin.