Pseudomonas Septicaemia and Ecthyma Gangrenosum

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SUMMARY

Pseudomonas aeruginosa is an important cause of life-threatening disease, especially in the immunologically compromised patient.

Four case reports of infants with Pseudomonas infection are presented, and attention is drawn particularly to the clinically recognizable skin lesions produced by the infecting organism.

A Gram-negative rod characterized by the production of a bluish-green pigment, the Pseudomonas also produces an endotoxin responsible for Gram-negative shock and three categories of exotoxin which cause, respectively, ecthyma gangrenosum, haemolytic anaemia and reticuloendothelial depression.

Treatment is a problem because of resistance to many antimicrobial agents. Regardless of therapy, the mortality rate for Pseudomonas infections remains very high.


Pseudomonas aeruginosa, formerly known as Bacillus pyocyaneus, is a Gram-negative motile rod found commonly in soil, dust, water, sewage, animal and human faeces, and in hospital kitchens, lavatories and intensive care units (ICUs). It has been isolated from the traps of sinks, baths and drains, and can survive in several antiseptic or disinfectant solutions. It may also be found on the skin, especially that of the perineum and axilla.

The organism grows readily on a wide variety of media under aerobic conditions with the formation of low, convex colonies which are greenish-blue in colour due to the production of a pigment, pyocyanine. Some strains produce pyorubin, while a small percentage do not produce obvious pigment.

Previously considered to be an insignificant organism and not highly pathogenic, the Pseudomonas has become increasingly important over the past 40 years as a cause of life-threatening disease, particularly in the immunologically compromised patient. The fatality rate in Pseudomonas septicaemia or bacteraemia has been documented in various reports as 20%, 49% and 67%.

Infections caused by P. aeruginosa include septicaemia, pneumonia, meningitis, osteomyelitis, pyelonephritis, ecthyma gangrenosum, abscesses, colonization of lacerations and burns, and otitis externa.

Several cases of Pseudomonas infection have been seen in the Paediatric Department of Baragwanath Hospital, Johannesburg. In these a notable feature was involvement of the skin and subcutaneous tissues, resulting in ecthyma gangrenosum. Four cases will be described, and the discussion which follows will deal with the pathophysiology and virulence of this organism, host defences and difficulties encountered in management.

CASE REPORTS

Patient 1

A girl aged 10 months was admitted to hospital with a 2-day history of cough and fever. She had had sores on her right leg for a week.

On examination she was found to be ill, and weighed 7,86 kg (just above the 3rd percentile). She had diarrhoea and bronchopneumonia, and bullous eruptions were noted on the right thigh and buttock.

The haemoglobin concentration was 10,3 g/dl, and it dropped to 8,8 g/dl over the next 2 weeks. The total white cell count was 7 700/μl initially, and was made up of 4% neutrophils, 16% monocytes and 80% lymphocytes. The neutropenia worsened over the next few days, neutrophils forming 1% of a total count of 5 400/μl. This was followed by a rise in the white cell count to 29 700/μl of which 64% were neutrophils, 6% monocytes, 28% lymphocytes and 2% eosinophils.

Culture of fluid from the skin lesions resulted in a growth of Enterobacter species and P. aeruginosa, the latter being sensitive to streptomycin, kanamycin, gentamicin, polymyxin and carbenicillin. P. aeruginosa was also grown from blood culture with a similar range of antibiotic sensitivity, which included tetracycline and chloramphenicol.

Treatment was initially commenced with lincomycin and gentamicin; carbenicillin was added when the culture results were available. After an initial deterioration the patient made steady progress. The bullae ruptured, leaving an erythematous base, and the lesions then became necrotic, and extended considerably in size (Fig. 1). Skin

Fig. 1. Patient 1: ecthyma gangrenosum on right leg and buttock.
Patient 2

A 6-month-old boy was transferred from a neighbouring tuberculosis hospital with a recent history of pyrexia, coughing and vomiting. For some time he had been receiving treatment for pulmonary tuberculosis (streptomycin, isoniazid and ethionamide).

He was underweight for age (4.65 kg), and displayed marked respiratory distress, with bilateral crepitations and wheezing. The child's condition deteriorated over the next 24 hours and he was then transferred to the ICU, where he was connected to a respirator. He remained critically ill over the next 2 weeks. Skin lesions appeared on the face, and the baby died the following day. Administration of antituberculous drugs had been continued and he was also given penicillin, cloxacillin and gentamicin. Carbencillin was commenced on the day before death, when *Pseudomonas* infection was suspected clinically.

On admission, the haemoglobin concentration was 12 g/dl. The level dropped later, necessitating repeated blood transfusions. The initial white cell count was 27 500/μl. Blood cultures were negative, but *P. aeruginosa* was cultured from the skin lesions. The organism was not recovered from any of the respirator equipment in the ICU.

Patient 3

A boy aged 1 year was admitted to hospital after having had diarrhoea and vomiting for 3 days. He had had measles 2 weeks earlier.

The child's weight was on the 3rd percentile. He was pyrexial, had loose stools, and a circular necrotic lesion was noted on the left nostril. The rest of the examination was non-contributory.

The haemoglobin concentration was 10.8 g/dl on admission; after 2 weeks it dropped to 6.8 g/dl, and a blood transfusion was given. The first white cell count was 15 000/μl (57% neutrophils, 2% monocytes, 41% lymphocytes), and subsequent counts were similar.

Culture from the nasal ulcer yielded *Escherichia coli* and *P. aeruginosa*; from a second culture a pure growth of *Pseudomonas* was obtained. The antibiotic sensitivity included polymixin, gentamicin and carbencillin, also streptomycin, tetracycline and chloramphenicol.

The first blood culture was negative, but 2 weeks after admission *Citrobacter freundii* was grown from the blood and also from a scalp abscess. A month after admission, a *Salmonella* organism was found in the stool.

Antibiotic treatment was commenced with ampicillin and gentamicin, followed by polymixin, carbencillin and gentamicin, and finally, a course of chloramphenicol.

Response to treatment was slow, diarrhoea and pyrexia persisted, and the general condition was poor. After about 1 week the ulcer on the nostril developed a purple edge and progressed to become a circular punched-out penetrating lesion. This finally contracted down to pinhole size as healing took place. The child was discharged well 5 weeks after admission.

Patient 4

A girl aged 10 months was discharged from another hospital after having spent more than 2 months there with persistent gastro-enteritis. During that time she also contracted measles and developed an ulcer on the buttock which had not healed. She was admitted to Baragwanath Hospital 1 week after discharge, still suffering from diarrhoea.

The child was alert but fretful. She weighed 5.43 kg (less than 60% of expected weight) and had features of kwashiorkor. Indurations on the thighs and buttocks were presumed to be the results of intramuscular injections. The chest was clear, the liver was palpable 2 cm below the costal margin, and the stools were very loose and mucoid. There was a 1.5-cm circular ulcer with undermined edges on the right buttock. Treatment was commenced with intravenous fluids, penicillin, gentamicin and cloxacillin.

Over the next few days the diarrhoea persisted, and recurrent dehydration occurred.

A severe purulent conjunctivitis developed 4 days after admission. By the following day the eyelids had purple, necrotic edges and this discoloration was also evident around the buttock ulcer, which was extending in size. The child was pale and jaundiced. *Pseudomonas* infection was suspected and appropriate therapy was instituted (Figs 2 and 3).

The septicaemic state resulted in a bleeding tendency in addition to haemolysis, for which repeated blood transfusions were required. Small-bowel perforation necessitated surgery. The infection, however, could not be brought under control. The ulcer on the buttock extended to include the perianal area and anus; the eyelids necrosed and sloughed away leaving the globes exposed, both of which were involved in a total panophthalmitis, and there was retro-orbital pus. The lower part of the nasal septum became gangrenous (Figs 4 and 5). Death occurred 3 weeks after admission.

The haemoglobin concentration on admission was 8.7 g/dl, decreasing to approximately 6 g/dl on 3 occasions, despite blood transfusions. The initial total white cell
count was 3 500/μl (21% neutrophils, 3% monocytes, 76% lymphocytes); a repeat count showed a total of 2 000/μl, but this later rose to 18 700/μl. Platelets were normal at first, but then decreased to 17 000/μl.

The blood cultures taken on admission were negative, and a repeat culture after 5 days yielded *P. aeruginosa*, which showed sensitivity to gentamicin and polymixin, but none to carbenicillin, and limited sensitivity to tetracycline and chloramphenicol.

The buttock ulcer yielded *Enterobacter* species and *Proteus mirabilis*. Pus from the eyes yielded *P. aeruginosa*, sensitive to gentamicin and polymixin, but little sensitivity to carbenicillin, and none to any other antibiotic.

**DISCUSSION**

**Pathophysiology**

In fulminating *Pseudomonas* septicaemia, the well-known picture of Gram-negative shock may become manifest, viz. hypothermia, hypotension, tachycardia, anuria, paralytic ileus and leucopenia. The endotoxin responsible for this effect is a protein-lipopolysaccharide complex contained in the cell wall of the organism. Hepatocellular damage can occur, resulting in jaundice, with elevation of both conjugated and unconjugated bilirubin.

In surface infections three categories of exotoxin can be isolated. Multiple cytotoxic enzymes released from the organisms result in focal necrosis of granulating tissue and marginal pyoderma gangrenosum through both a direct action and by thrombosis of blood vessels. In addition, haemolysins are produced which initiate a sudden and severe haemolytic anaemia. A third exotoxin acts as an inhibitory factor, causing a relative paralysis of the reticulo-endothelial system, manifested by leucopenia, impaired antibody response to administered foreign antigens, and the presence of bacteria more invasive than the *Pseudomonas* in the patient's blood. In a review of 108 cases of *P. aeruginosa* bacteraemia it was found that 32 episodes of bacteraemia had occurred before, at the same time or after the *Pseudomonas* bacteraemia.

Virtually all of the above features were evident in the 4 cases reported. Particularly helpful in making the diagnosis of *Pseudomonas* septicaemia in these patients were the characteristic skin lesions known as ecthyma gangrenosum. These lesions may be single, but are usually
multiple and isolated. They commence as erythematous or purpuric macules which increase in size, develop into haemorrhagic bullae, then ulcerate to form lesions with necrotic centres and haemorrhagic borders. Histopathological examination shows a necrotizing vasculitis with a remarkable absence of neutrophilic infiltration.4,5 Identical lesions have been described in association with P. cepacia endocarditis.6

**Individuals at Risk**

*P. aeruginosa* is an organism which does not normally cause disease in the healthy host, but may produce infection when body defences are compromised, and in such circumstances it is described as an opportunist. Gram-negative bacilli are particularly important as causes of opportunistic infections resulting in life-threatening disease, and of these *Pseudomonas* is the most serious, in that it results in the highest mortality.1 One reason for its upsurge in recent years is its predilection for debilitated patients, especially when immune responses are impaired either by the disease process or by therapy, e.g. patients with cystic fibrosis, organ transplants, leukaemia, cancer, severe burns, immunological deficiency syndromes, congenital neutropenia, or those on immunosuppressive therapy.1,4 Other patients at risk are those in ICUs, especially if they are on respirators,16 and those with intravenous cannulation.1 Another important factor is the use of antimicrobial drugs which eliminate other organisms, allowing overgrowth of the *Pseudomonas* organisms against which these drugs are ineffective.1

In the review by Flick and Cluff7 the sites of initial infection in approximately 75% of the 108 patients with *Pseudomonas* bacteraemia were respiratory tract, urinary tract, skin and intravascular catheters, and 27 of the patients had received at least one immunosuppressive drug or radiotherapy.

**Host Defence and Virulence of the Organism**

The mechanism by which the host defends itself against *Pseudomonas* infection is unknown, but it has been considered to be largely by granulocyte activity associated with humoral antibody and complement. But in those immunologically compromised individuals who are at risk of life-threatening disease from *Pseudomonas* infection, it is mainly the cell-mediated immunity which is severely depressed. Munster and Leary9 reported a study on healthy volunteers which demonstrated the presence of cell-mediated immunity mounted against *P. aeruginosa* in addition to a rise in haemagglutinin titres. Cell-mediated immunity could well have a biological role in host defence. Children with kwashiorkor have depressed cellular immunity,13 and therefore would be at greater risk for opportunistic infection by *P. aeruginosa* if cellular immunity does indeed play a part in natural defence mechanisms.

In a postmortem study of Black children in a respiratory intensive care unit,7 it was shown that *P. aeruginosa* was the most common opportunistic pathogen, and it usually complicated a viral infection. Autopsies on 5 children with *Pseudomonas* infection showed lung changes suggestive of viral infections, but no polymorphonuclear infiltration. It was postulated that polymorphonuclear leucocyte function may have been impaired by the infecting viruses in these children. It has previously been shown that infections with influenza virus, measles and respiratory syncytial virus (RSV) result in defective polymorphonuclear motility. Reduced phagocytosis and intracellular killing have also been observed in influenza and RSV infections.7 Thus, viral respiratory infections which impair normal defence mechanisms predispose to *Pseudomonas* superinfection.

Another factor in the virulence of *Pseudomonas* is its ability to produce a C1-cleaving enzyme, resulting in a local C3 deficiency state which protects it from attack.10

Reference has already been made to the effects produced by the endo- and exotoxins of this organism.

**Antimicrobial Agents**

Many strains of *P. aeruginosa* show in vitro resistance to a wide range of antimicrobial agents, and multiple resistance is common.11 The most effective drugs are carbenicillin, polymixin and the aminoglycosides, but resistance to these drugs may also occur. In the study by Flick and Cluff,4 226 isolates were obtained. All but 9 were sensitive to the drugs mentioned above; these 9 were resistant to gentamicin and/or carbenicillin and/or polymixin. Only one isolate was sensitive to chloramphenicol, and one to streptomycin.

Aminoglycosides are at present the most effective agents against *Pseudomonas*, but resistance to gentamicin does occur and to a lesser extent to tobramycin also, while susceptibility to amikacin seems so far to remain unimpaired.15 In vitro studies have shown a synergistic action between carbenicillin and the aminoglycosides.7

**CONCLUSION**

Ecthyma gangrenosum is an important manifestation of *Pseudomonas* septicaemia, and since it may appear before organisms are isolated from the blood appropriate therapy should be commenced directly such a lesion is recognized.4

Regardless of therapy, however, the mortality rate for *Pseudomonas* infections remains very high. This is undoubtedly the result of three adverse factors:

1. The host — affected patients are usually debilitated and immunologically compromised.

2. The organism — a virulent microbe by virtue of its ability to counteract natural host defences and to produce Gram-negative shock.

3. The therapy — very few antimicrobial agents are effective, and resistance to all may develop.

The cases reported illustrate the problems in management resulting from these factors.
REFERENCES

Pneumothorax Complicating Acute Asthma
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SUMMARY
The association of asthma and pneumothorax in hospital practice is examined. The association varies from 1:300 to 1:1000 acute asthmatics admitted to either a specialized or general unit. The clinical details of 18 patients with further reference to associated parenchymal lung diseases are discussed.

First recognized by Laennec1 in 1819, and first noted as a complication of childhood asthma in 1850,2 only 20 cases of pneumomediastinum, or pneumothorax, or both, complicating acute asthma in children had been reported in the world literature by 1960.3 Subsequent work by various authors,4-6 suggests that these conditions complicate childhood asthma more frequently than was formerly suspected. The incidence of the association of asthma and pneumothorax has not been described from adult chest units. An exception is a paper from the Mayo Clinic by Legge et al.7

A paper by Karetsky8 created a controversy in Britain when he attributed the death of 2 patients in status asthmaticus with pneumothorax to the favoured British therapy of intermittent positive pressure breathing. A 25% mortality rate was quoted when pneumothorax complicated an episode of acute bronchospasm. It was decided to analyse statistics gathered in Birmingham, UK.

PATIENTS AND METHODS
Personal surveys were made of patients in the respiratory units at the East Birmingham and Queen Elizabeth Hospitals. Computer recorded data were available for the medical units serving the other Birmingham City Hospitals (1 x 10⁶ people) and for the units serving the hospitals of the wider Birmingham Regional Hospital Board (5.25 x 10⁶ people). Patients for whom the diagnostic label 'bronchial asthma' appeared on the case notes were cross-referenced against all patients found on admission to have a pneumothorax. All case notes from the personal survey meeting these criteria were examined, as were all case reports obtained from the computer survey for the year 1972. This year was considered by the Regional Statistical Analyst to be the most accurately recorded period for the region. Case reports from the Birmingham City Hospitals for the years 1965-1969 inclusive were also examined. Eighteen case reports in all were scrutinized.

RESULTS
Statistics for the years 1963-1972 inclusive were available for the East Birmingham Respiratory Unit. Fourteen hundred and eight patients diagnosed as having bronchial asthma were admitted. Three hundred and seventy-three patients were admitted with a pneumothorax (excluding surgical cases) and nine of these (0.63%) had both asthma and pneumothorax. Five patients with both pneumothorax and asthma (0.32% of all asthmatics) were admitted to...