



Antibiotics - Papua New Guinea

THE USE OF ANTIBIOTICS IN CHILDREN IN PAPUA NEW GUINEA (PNG)

by

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I. INTRODUCTION

The use of antibiotics in children in PNG will be discussed under two headings - outpatient treatment and inpatient treatment. Neonates will not be considered. Quite appropriately, a lot of attention has been given to the management of children in Papua New Guinea with life-threatening sepsis, such as meningitis and severe pneumonia. However outpatients are an important group too. They make up the large majority of children treated with antibiotics. Even if only because of the large amounts of antibiotics used in their management, outpatients deserve more attention than they have received in the past.

II. OUTPATIENTS

1. Outpatients - diseases treated

In order to determine the indications for the administration of antibiotics to outpatients, a record was made of the diagnosis of 100 consecutive children given antibiotics at the Goroka pediatric outpatient clinic. The results are shown in Table I. Three diseases accounted for 97% of the antibiotic use. One half of the children were treated for mild pneumonia, one quarter for otitis media and one quarter for skin infection.

Table I

Indication for antibiotic treatment
of 100 consecutive pediatric outpatients

Mild pneumonia	47
Otitis media	27
Skin infection	23
Other	3

In these cases the aetiology of mild pneumonia is unknown, but a previous lung aspirate study has shown that in children with consolidation on a chest X-ray, the pneumonia is caused by *Haemophilus influenzae* and/or *Streptococcus pneumoniae*. For the present, it can only be assumed that these two organisms are also the usual cause of mild pneumonia in PNG children. Overseas studies have found that about two-thirds of cases of acute otitis media are due to the same two organisms. (1) There has been little work on the bacteriology of skin sores in PNG children - this is a field that merits investigation. Thus, in treating pediatric outpatients in PNG, prime consideration has to be given to the antibiotic sensitivities of *Haemophilus influenzae* and *Streptococcus pneumoniae*.

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2. Outpatients - which antibiotic

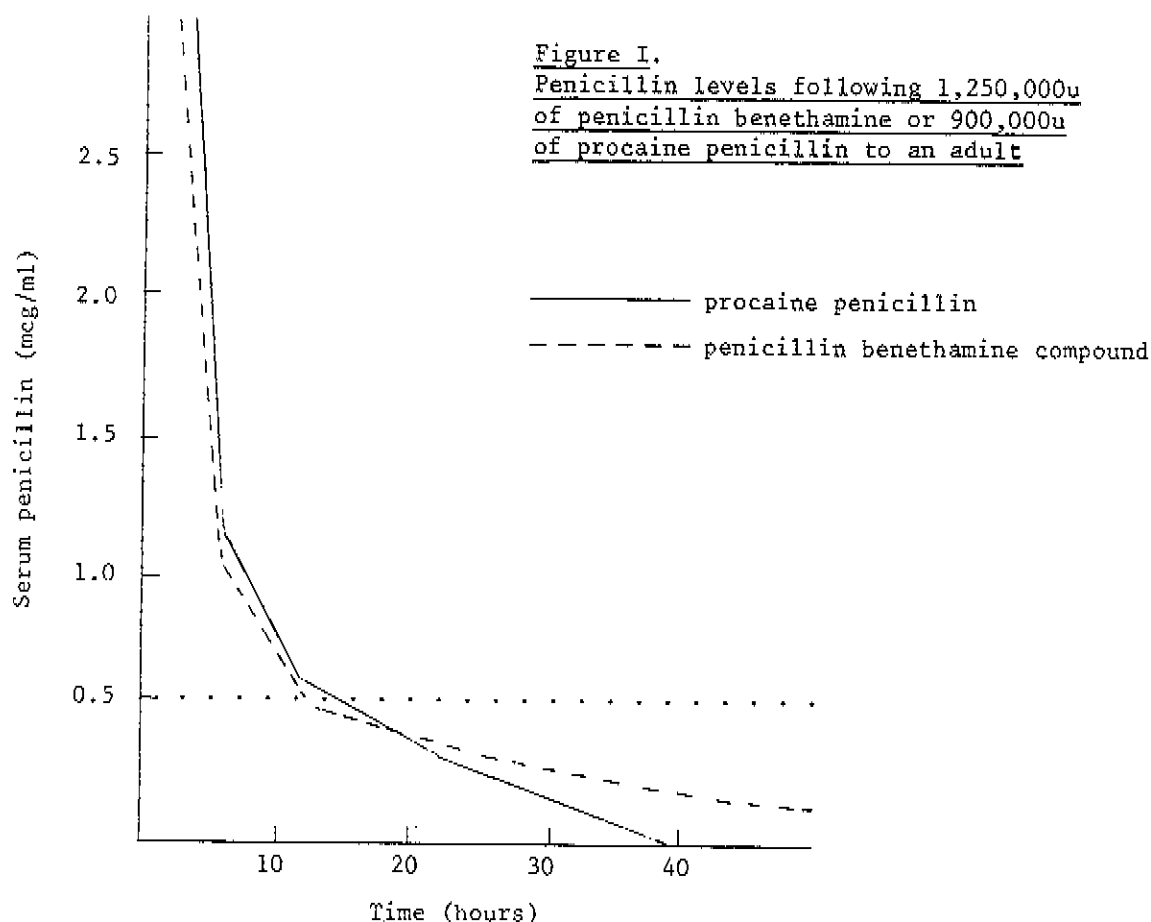
Penicillin is the drug of choice for outpatient treatment of children in PNG, provided it is effective against *Haemophilus influenzae* and *Streptococcus pneumoniae*. It is cheap and safe, and can be given once a day if a depot preparation is used. An injectable antibiotic has advantages in small children - oral drugs may be spat out or vomited. Benzyl penicillin is four to eight times more active against *Haemophilus influenzae* than phenoxymethyl penicillin,⁽²⁾ so that phenoxymethyl penicillin (penicillin V) should not be used to treat this organism. In vivo susceptibility studies show that *Haemophilus influenzae* is almost as sensitive to benzyl penicillin as it is to ampicillin.⁽¹¹⁾

In most parts of Papua New Guinea it is probably necessary to have each dose of antibiotic given by a health worker. This means that doses cannot be given more often than once a day to outpatients, and limits the choice of antibiotic to one with a long half life. Apart from depot penicillin, other possibilities are trimethoprim, a long-acting sulphonamide, cotrimoxazole, streptomycin and chloramphenicol in oil. Since trimethoprim is not very active against pneumococcus and sulphonamides may not kill all *Haemophilus* (because of previous widespread use of sulphonamides for diarrhoea in PNG), it would probably be necessary to use cotrimoxazole, which is about three times as expensive as procaine penicillin (see Appendix). There are plans to investigate the sensitivity of *Haemophilus influenzae* to sulphonamides. Pneumococci are often resistant to streptomycin, and the drug should be reserved for use in tuberculosis and neonates. Chloramphenicol must be reserved for use in patients with severe sepsis.

3. Outpatients - which IM penicillin

Cultures of lung aspirates and blood samples were done from about 70 children admitted to Goroka Hospital with pneumonia. Most of the children studied had not had antibiotics before admission. *Haemophilus influenzae* had grown in about 40% of cases and *Streptococcus pneumoniae* in about 35% of cases. In 15 (60%) of 25 strains of pneumococcus tested, the minimum inhibitory concentration (MIC) of penicillin was 0.1 mcg/ml or more. An MIC of 0.1 mcg/ml represents a ten-fold increase over the usual MIC of 0.01 mcg/ml of penicillin for pneumococci. Eight (32%) of the 25 strains had an MIC of 0.5 mcg/ml or more. The MIC of penicillin against *Haemophilus influenzae* is usually 0.5-2.0 mcg/ml. Thus it appears likely that 0.5 mcg/ml is the minimum concentration of penicillin needed to inhibit (not kill) a large proportion of the organisms being treated in pediatric outpatients. It is, of course, highly desirable to maintain much higher levels of penicillin than this for as long as possible.

The present Standard Treatment of mild pneumonia and otitis media is either aqueous procaine penicillin daily for five days, or penicillin benethamine compound IM every second day for three doses. The serum level of penicillin following 1,250,000u of penicillin benethamine⁽³⁾ or 900,000u of procaine penicillin⁽²⁾ to an adult are shown in Fig. I. It can be seen that both injections give penicillin levels over 0.5 mcg/ml for a similar length of time (about 15 hours). Little is known of serum penicillin levels in children following different doses of procaine and benethamine penicillin. At present Medical Stores' Catalogue prices, it costs US\$1.11 for three ampoules of penicillin benethamine and only US\$0.36 for five 900,000 doses of procaine penicillin (see Appendix). Moreover, the prolonged low levels of penicillin following an injection of penicillin benethamine may well lead to the emergence of even more resistance to penicillin.⁽⁴⁾ Thus, a course of aqueous procaine penicillin is one-third the price of penicillin benethamine, and a single injection maintains therapeutic levels for the same period as the latter.



4. Outpatients - compliance

In order to determine the level of compliance amongst children prescribed five days of procaine penicillin injections, the number of children returning for each injection at Goroka pediatric outpatients over a 12-day period was recorded. The results are shown in Table II. The number returning for penicillin benethamine injections was too small to be interpreted. Of eleven children, seven (64%) received only one injection, three (27%) received each of two prescribed injections and one (9%) received two of three prescribed injections.

It may be preferable to recommend three rather than five days of procaine penicillin for outpatients. There might be better compliance, and perhaps a double dose could be given (half into each buttock) on the third day. Consideration may have to be given to changing the dilution of procaine penicillin yet again - to 5ml of water rather than 10ml of water. There are plans to perform a prospective trial at Goroka outpatients of a variety of penicillin regimens. *Haemophilus influenzae* has never been very sensitive to penicillin, and many pneumococci now show increased resistance to penicillin. These are the two main pathogenic bacteria in PNG children. Standard Treatments will have to provide high levels of penicillin.

Table II

Number of children returning for 5 days' penicillin

	Day				
	1	2	3	4	5
Mild pneumonia	162(100%)	107(66%)	79(49%)	47(29%)	29(18%)
Otitis media	83(100%)	50(60%)	34(41%)	21(25%)	13(16%)
Skin infection	63(100%)	42(67%)	22(35%)	14(22%)	7(11%)
TOTAL	308(100%)	199(65%)	135(44%)	82(27%)	49(16%)

III. INPATIENTS

1. Inpatients - diseases treated

Pneumonia and meningitis are the two most important diseases treated with antibiotics in pediatric inpatients in PNG. In the decade 1970-79, these two diseases accounted for 32% of the admissions to Goroka children's ward and for 42% of the deaths. Again, *Haemophilus influenzae* and *Streptococcus pneumoniae* cause the majority of these two diseases in Goroka children.

2. Inpatients - which antibiotic

The Standard Treatment of moderate pneumonia in children has long been benzyl penicillin intramuscularly every six hours. This is usually effective, but it is possible that an increasing proportion of children fail to respond to benzyl penicillin and require treatment with chloramphenicol. This is consistent with the increasing resistance of pneumococci to penicillin in Papua New Guinea .(4, 12)

In the past, children with meningitis and severe pneumonia have been treated with penicillin (for pneumococcus and meningococcus) plus chloramphenicol (for *Haemophilus*). However some trials showed that there is no advantage in giving both penicillin and chloramphenicol in either of these diseases - there may even be antagonism between these two antibiotics. Chloramphenicol alone is cheaper and more convenient. In a trial on meningitis treatment intramuscular chloramphenicol alone was at least as effective as intravenous penicillin plus chloramphenicol. The third edition of the PNG pediatric Standard Treatment Book therefore recommends intramuscular chloramphenicol alone for the initial treatment of meningitis and severe pneumonia.

No drugs other than chloramphenicol and penicillin need to be considered for the initial treatment of meningitis and severe pneumonia in children. Ampicillin is 2.6 times as expensive as chloramphenicol (see Appendix), tetracycline causes staining of the teeth in small children and the aminoglycosides cross the blood-brain barrier poorly and may mask tuberculosis. Aplastic anaemia following chloramphenicol appears to be very rare in PNG. Even if the incidence were as high as 1 in 20,000 children treated, (2) this has to be compared with the mortality of 20% (4,000 in 20,000) from meningitis and severe pneumonia.

3. Inpatients - interactions with chloramphenicol

The Standard Treatment of meningitis in PNG children had been intravenous fluids, penicillin, chloramphenicol, phenobarbitone and antimalarials. About 90% of a dose of chloramphenicol is excreted in the urine, after conjugation with glucuronic acid in the liver. (5) Phenobarbitone is a potent inducer of glucuronyl transferase (hence its use in

jaundiced neonates). It has recently been shown that administration of phenobarbitone in addition to chloramphenicol doubles the rate of excretion of chloramphenicol, leading to subtherapeutic blood levels unless the dose is increased.⁽⁵⁾ Phenytoin toxicity is very common if it is given with chloramphenicol.⁽⁶⁾ Therefore, patients being treated with chloramphenicol should not be given phenobarbitone or phenytoin - convulsions should be treated with paraldehyde. Two studies in rats suggest that paraldehyde and chloramphenicol can safely be used at the same time.⁽⁷⁾ A study on serum levels of chloramphenicol in children given paraldehyde will be done.

Paracetamol has recently been shown to prolong the half life of chloramphenicol from 2-3 hours to 18-24 hours.⁽⁸⁾ There is evidence of antagonism between chloramphenicol and aminoglycosides.⁽⁹⁾ Chloramphenicol should not be given at the same time as paracetamol or aminoglycosides.

4. Inpatients - overuse of chloramphenicol

At present chloramphenicol is used for the clinical management of meningitis, severe pneumonia, septicaemia, osteomyelitis and pigbel.* The alternatives to chloramphenicol are inferior on grounds of cost and efficacy. It is important that the use of chloramphenicol be restricted to patients with severe sepsis, so that the emergence of resistant organisms will be delayed as long as possible. The use of chloramphenicol could be reduced somewhat by using erythromycin to render children admitted with pertussis noninfectious. Erythromycin suspension 50mg/kg per day is the same price as the equivalent dose of 100mg/kg per day of chloramphenicol suspension (see Appendix).

IV. THE BIG FOUR

Pneumonia, gastroenteritis, meningitis, malaria and acute respiratory infections account for 40% of all hospital deaths in PNG.⁽¹⁰⁾ These diseases represent a large proportion of the curable disease in PNG, and they can all be effectively and cheaply treated with penicillin, chloramphenicol, antimalarials and rehydration fluids - the Big Four. There is little point in having health services at all without the Big Four.

In 1978 PNG spent only 6% of the Health Budget on pharmaceutical materials and supplies. This is a low proportion. The drug supply system is extremely efficient, but the money allocated to the supply of drugs is inadequate. An adequate supply of the Big Four drugs to all parts of the country at all times must be ensured.

V. CONCLUSION

Bacterial infections are a major cause of death in Papua New Guinea children. Our increasing knowledge about the causative organisms and their sensitivities has enabled us to design prospective controlled trials to improve the management of these diseases. Much further research remains to be done, but already Standard Treatments have been improved as a result of this knowledge. Adequate supplies of essential drugs to the whole of PNG must be ensured. It is to be hoped that eventually effective vaccines will enable many of these diseases to be prevented.

* Necrotizing enteritis affecting the small intestine caused by *Clostridium welchii*, type C and its B toxin. It is endemic in the highlands of Papua New Guinea (WHO, Weekly Epid. Rec., 1978, 21: 152)

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SUMMARY

Of children treated with antibiotics at Goroka outpatients, one-half have mild pneumonia, one-quarter have otitis media and one-quarter have skin infection. Most cases of mild pneumonia and otitis media are probably due to *Haemophilus influenzae* or *Streptococcus pneumoniae*. Standard Treatments will have to provide high serum levels of penicillin. Pneumococci with increased resistance to penicillin and *Haemophilus influenzae* usually have an MIC of 0.5-2.0 mcg/ml of penicillin. Serum penicillin levels in adults stay above 0.5 mcg/ml for about 15 hours after 900,000u of procaine penicillin or 1,250,000u of penicillin benethamine compound administered intramuscularly, but three injections of penicillin benethamine cost three times as much as five injections of aqueous procaine penicillin. Only 16% of children attending Goroka outpatients return for five doses of procaine penicillin. Perhaps outpatients should be given higher doses of procaine penicillin for three days.

Pneumonia and meningitis are the most important diseases requiring antibiotics in pediatric inpatients in PNG. Most cases are due to *Haemophilus influenzae* or *Streptococcus pneumoniae*. Prospective trials in PNG children have shown chloramphenicol alone to be at least as effective as penicillin plus chloramphenicol for meningitis and severe pneumonia. Phenobarbitone, paracetamol and aminoglycosides should not be given to patients on chloramphenicol. The use of chloramphenicol should be restricted to patients with severe sepsis, so that the emergence of resistant organisms will be delayed as long as possible.

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THE COST OF ANTIBIOTICS IN PAPUA NEW GUINEA

Oral antibiotics - cost of five days' treatment (US\$)

	<u>Cap/Tab</u>	<u>Susp</u>	<u>Dose</u>
Oxytetracycline	0.23	-	250mg QID
Phenoxymethyl pen.	0.29	1.23	250mg QID
Chloramphenicol	0.31	1.67	250mg QID
Sulphadimidine	0.37	-	1g QID
Ampicillin	0.77	2.25	250mg QID
Cotrimoxazole	0.94	-	2 tab BD
Erythromycin	1.39	3.70	250mg QID
Cloxacillin	2.86	-	250mg QID

Parenteral antibiotics - cost of five days' treatment (US\$)

	<u>Injection</u>	<u>Dose</u>
Procaine penicillin	0.36	900,000u daily
Streptomycin	0.77	1g daily
Penicillin benethamine	1.11	3 ampoules
Chloramphenicol	1.54	250mg QID
Benzyl penicillin	1.84	1 mega QID
Sulphadimidine	3.09	1 gram QID
Oxytetracycline	3.70	200mg IM BD
Ampicillin	4.01	250mg QID
Cloxacillin	4.63	250mg QID
Kanamycin	6.79	500mg BD
Gentamicin	12.73	80mg TDS

Source: PNG Medical Stores Catalogue, Fifth Edition, 1980

Abbreviations: BD - twice a day
TDS - 3 times a day
QID - 4 times a day

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