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Antibiotic-resistant bacterial sepsis in Papua New Guinea

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SUMMARY

Infections due to antibiotic-resistant bacteria, especially gram-negative bacteria, are a common cause of child mortality in Papua New Guinea. Antibiotic-resistant bacteria include the enteric gram-negative bacilli, especially *Escherichia coli*, *Klebsiella* and *Enterobacter*, and *Haemophilus influenzae* type b, a major respiratory tract pathogen and cause of meningitis. Among these bacteria there is now high-level resistance to standard antibiotics, including chloramphenicol, amoxycillin and cotrimoxazole. Reasons behind the increase in antibiotic-resistant bacterial infections are the widespread unregulated use of antibiotics and the very large burden of bacterial infections. Risk factors for development of resistant enteric gram-negative infections include village births, prolonged hospital stay, kwashiorkor in adopted children and previous treatment with broad-spectrum antibiotics. Cost-effective strategies to combat these pathogens will need to be broad and must focus on reducing the use of antibiotics for trivial illnesses, reducing the need to use antibiotics and reducing the risk factors for resistant bacterial sepsis. There must be stricter regulation of commercial pharmacies, education of health workers on how to avoid inappropriate antibiotic prescribing, a focus on the prevention of pneumonia by immunization with new vaccines, improvements in the quality and uptake of formal maternal care services and public health measures within villages. In addition there is a need for better surveillance for antibiotic-resistant bacteria within hospitals; this will require substantial improvements in laboratory facilities and carefully planned research collaboration. A national committee should be established to advise on these matters and coordinate interventions.

Introduction

Infections caused by antibiotic-resistant bacteria among children in highlands Papua New Guinea (PNG) are increasing in incidence (1). Mortality from antibiotic-resistant bacterial sepsis is disproportionately high, relative to the incidence. Two processes must be active for the development of resistant infections: first, the development of antibiotic resistance in intrinsically susceptible bacteria; and second, host invasion or the spread of the bacteria to another person. In this review I outline the scope of the problem among children in PNG; the likely causes for the emergence and spread of bacterial strains that are resistant to standard antibiotics; the difficulties of controlling spread of these bacteria, particularly in PNG; and where solutions to this problem may be. I suggest 11 practical interventions that would help to combat this problem.

The magnitude of the problem

At Goroka Hospital between April 1998 and March 2000, multiresistant enteric gram-negative sepsis occurred in 106 of 5331 paediatric admissions (2%), but caused 87 (25%) of 353 deaths. High-level resistance was found to all standard antibiotics: among the 133 isolates from blood or cerebrospinal fluid (CSF) cultures obtained from 116 children between October 1997 and March 2000, 89% were resistant to chloramphenicol, 62% to gentamicin, 94% to amoxycillin, 86% to cotrimoxazole, 45% to kanamycin, 60% to tetracyclines, 7% (3 out of 46 isolates tested) to ciprofloxacin and 19% (25/129) to ceftriaxone. So far *Salmonella typhi* is the only enteric

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gram-negative bacillus not to have acquired widespread resistance to chloramphenicol (2). Although not well explained, this is very fortunate. The massive increase in cases of typhoid in the last 15 years is a comment on the poor state of public health in the highlands, and an example of how enteric bacteria can spread (3,4). Development of chloramphenicol-resistant typhoid would be a major public health disaster leading to considerable mortality.

Haemophilus influenzae type b (Hib), a non-enteric gram-negative cocco-bacillus, causes 40% of meningitis and 7-20% of cases of pneumonia. Penicillin-resistant Hib was first reported in PNG in 1982 (5). Recent Hib isolates from cerebrospinal fluid at Goroka show increasing resistance to chloramphenicol (Table 1), and a similar pattern is emerging in Port Moresby (6). Variable but increasing rates of chloramphenicol resistance have been reported internationally (7), with resistance found in more than 50% of Hib isolates in India (8). Although there is little evidence to date that chloramphenicol resistance in Hib leads to treatment failure in pneumonia, the risk of death or severe neurological sequelae in chloramphenicol-resistant Hib meningitis is much greater if chloramphenicol rather than a third-generation cephalosporin is used.

In 1980 one-third of blood-culture or CSF isolates of *Streptococcus pneumoniae* from children with severe pneumonia in Port Moresby were penicillin insensitive (9). In other countries intermediate resistance to penicillin has not been associated with treatment failure with benzylpenicillin (10,11). Chloramphenicol-resistant pneumococci are much less common than penicillin-resistant strains. However, meningitis caused by penicillin-resistant pneumococci will almost always fail to respond to treatment with chloramphenicol (12) and a third-generation cephalosporin will be required. Fortunately these strains appear uncommon in PNG and caused only 3 cases of meningitis in Goroka between October 1997 and May 2000.

Chloramphenicol resistance among *Staphylococcus aureus* was first reported in 1979 (13). Although much less common than antibiotic-resistant Hib or enteric gram-negative bacilli, community-acquired methicillin-resistant *S. aureus* (resistant to flucloxacillin and chloramphenicol) has caused 3 child deaths at Goroka since 1998 (unpublished data).

Aetiology of bacterial resistance

Widespread use of broad-spectrum antibiotics

The widespread use of antibiotics, particularly of amoxycillin, trimethoprim-suphamethoxazole (cotrimoxazole) and chloramphenicol, over the last three decades has led to massive selection pressure for emergence of resistant bacteria. This is not to say that most of the antibiotic use has been inappropriate; there is a large burden of bacterial infections in PNG, as in other

TABLE 1

NUMBER OF HIB ISOLATES FROM CEREBROSPINAL FLUID AT GOROKA HOSPITAL, AND PERCENTAGE RESISTANT TO CHLORAMPHENICOL

Year	No of CSF Hib isolates	No (%) of chloramphenicol-resistant isolates
1997	14	3 (21.4)
1998	27	4 (14.8)
1999	11*	4 (36.4)
2000 (January-March)	14	4 (28.6)
Total	66	15 (22.7)

* including one case of septic arthritis and pneumonia, isolated from joint aspirate

developing countries, that require treatment. However, some detrimental prescribing practices that can be implicated in the development of resistant strains have developed, the background to which requires some consideration.

Pneumonia, which causes more than 30,000 health facility admissions each year (14), is often treated in health centres and outpatient clinics now with a single dose of intramuscular benzylpenicillin, chloramphenicol or amoxycillin, followed by oral amoxycillin or cotrimoxazole prescribed for 5 days. A decade ago a five-day course of procaine penicillin was the standard treatment for mild or moderate pneumonia. This change has occurred primarily because of the withdrawal of procaine penicillin from standard treatment in 1996. This current practice also reflects misconceptions about the relative duration of action of single doses of antibiotics, and the sporadic way basic health facilities are open and primary health services are currently conducted. Procaine penicillin is a narrow-spectrum, long-acting penicillin that was shown to be very effective treatment for pneumonia of mild-moderate severity. When given as a once-daily intramuscular injection blood levels are satisfactory to treat *Streptococcus pneumoniae* and *Haemophilus influenzae*, the major pathogens causing pneumonia, for 24 hours after administration (15). Procaine penicillin was withdrawn in PNG because of a few cases of anaphylactoid reaction with one preparation of the drug, and because of concerns that the use of a multi-dose vial preparation may contribute to the transmission of HIV infection. It was also felt that replacement of a parenteral by an oral treatment would reduce the risk of HIV transmission through contaminated needles. Oral amoxycillin was the recommended alternative, partly because of the emergence of *Streptococcus pneumoniae* that had intermediate resistance to penicillin (9). For oral amoxycillin to be effective the parent (usually the mother) must understand the importance of compliance with oral medications. The correct dose needs to be given at the correct time intervals, and the infant needs to swallow the medicine without vomiting. Teaching mothers how to effectively give medicines is beyond the practice of many health workers, and it is highly doubtful that relatively uneducated rural mothers (and for that matter their urban sisters) administer oral medication correctly. Many children receive inadequate doses, and courses of inadequate duration. Previously all a mother needed to do was take the infant to the health facility each day for 5 days (for an injection of procaine penicillin). This also gave an important opportunity for the health worker to assess the progress of the child, and refer if the child was not improving. The use of broader-spectrum antibiotics, such as amoxycillin and cotrimoxazole, given orally, increases the likelihood of the emergence of resistance in other non-pneumonia pathogens (such as enteric gram-negative bacilli) (16). Many children now present with severe pneumonia after having been prescribed oral amoxycillin or cotrimoxazole, when a diagnosis of moderate pneumonia was made at health centres. In 632 children at Goroka with severe pneumonia in whom a history of prior antibiotic use could be recalled by the parent or was recorded in the health book, 149 (24%) and 42 (7%) had been prescribed amoxycillin and cotrimoxazole respectively in the previous week (unpublished data).

As is common worldwide oral amoxycillin or cotrimoxazole are frequently prescribed for trivial illness, particularly upper respiratory tract infections, for which there is no evidence of any value, but considerable evidence for adverse effects associated with antibiotic use (17,18). In PNG the most appropriate outpatient treatment for pneumonia has been withdrawn, and many health centres do not admit children for inpatient treatment (where they could also receive a narrow-spectrum penicillin, every 6 hours) because of staffing shortages, lack of water and other problems.

Over the last decade more commercial pharmacies are selling drugs without prescriptions. This unregulated practice has led to excessive and inappropriate use not only of standard antibiotics including oral chloramphenicol, but also of newer non-standard antibiotics including first- and second-generation cephalosporins and ciprofloxacin. This community pool of higher-generation antibiotics will lead to the next generation of resistance.

Lack of data on bacterial resistance patterns

The only data on antibiotic resistance come from Port Moresby and Goroka, because these are the only centres where bacteriology can be done to that level. It is highly unlikely that these are the only centres where the problem of multidrug resistance exists. Lack of bacteriology facilities in most rural base hospitals means that antibiotic-resistant infections go undetected. Deaths resulting from such infections are likely to be documented as unexplained, or may be attributed to other, noninfectious causes. This widespread 'ignorance' contributes to the uncontrolled spread of resistant bacteria. If antibiotic resistance cannot be recognized as a problem, then containment strategies will not be put in place.

Aetiology of bacterial spread

Cross-infection and nosocomial acquisition of resistant bacteria

Nosocomial transmission of bacteria is an ever-present problem that is difficult to avoid. Nosocomial infections, mostly due to resistant enteric gram-negative bacilli, occurred in 10% of child deaths at Goroka over 2 years (unpublished data); however, only 20% of all such infections had an identifiable source or were classified as potentially avoidable (injection site abscesses, surgical wound infections etc). Hospital wards in PNG are crowded with debilitated and immune-suppressed patients, most suffering from infectious diseases, most receiving broad-spectrum antibiotics. Strategies that have been proven elsewhere to limit spread of bacteria in hospitals are hand-washing, increasing space between beds, increased nurse-patient ratios, and use of narrow- rather than broad-spectrum antibiotics. Only hand-washing and use of narrow-spectrum drugs are within reach in PNG at this time. Nurse-patient ratios are fixed by the number of available trained staff, salary funding and patient numbers: factors that are unlikely to change in the short term. Increasing space between beds can only occur when admission numbers fall, length of stay is shortened or larger wards are built. Even simple hand-washing is problematic. Fundamental hygiene problems exist in some hospitals (19). Many district hospitals are dilapidated, dirty and have sporadic water supplies. Many health centres and some hospitals do not have inpatients because of the lack of running water. The government medical stores rarely have cleaning agents or soaps, so unless a health facility buys its own supplies and has running water, effective hand-washing will rarely occur. Inadequate toilet facilities and lack of running water make some district hospitals look like makeshift refugee camps, where enteric diseases spread rapidly.

In a neonatal unit in The Netherlands the use of narrow-spectrum antibiotics (benzylpenicillin) instead of broad-spectrum drugs (amoxycillin or third-generation cephalosporins) decreased colonization with resistant bacteria (16). This may provide an important lesson for future standard antibiotic protocols for common infections in PNG.

Vertical transmission of infection and the problem of village deliveries

In a cohort of 126 consecutive neonates who died in Goroka between April 1998 and March 2000, the greatest risk factor for gram-negative sepsis, which occurred in 30 (34%), was village birth (odds ratio 6.5, 95% confidence interval 2.5-16.9). It is likely that when delivery takes place without a clean technique the mother's enteric bacteria colonize the baby at or around the time of birth. The association between village deliveries and death from gram-negative sepsis may also be explained by poor post-natal hygiene practices. A study from India showing a 50% reduction in mortality from sepsis when gentamicin and cotrimoxazole were given to septic neonates in villages suggests that gram-negative sepsis is a major cause of neonatal mortality in other impoverished developing countries also (20).

The dilemma of third-generation cephalosporins

The solution to antibiotic resistance will not be found in better antibiotics. Third-generation cephalosporins, one major class of drugs effective against most multiresistant enteric gram-negative bacilli, and against chloramphenicol-resistant Hib, are expensive, and with widespread use resistance develops rapidly (16). Ceftriaxone costs K12.95 for a 1 g vial. This compares to K1.75 for a 1 g vial of

chloramphenicol or K0.71 for a 20 mg vial of gentamicin. To treat a 7 kg child for meningitis for 10 days with ceftriaxone currently costs K90.65, compared with K12.25 for 10 days treatment with chloramphenicol. Hib causes 40% of all cases of meningitis, and 30% of Hib meningitis are resistant to chloramphenicol. A change to a strategy of using ceftriaxone for all cases of meningitis would lead to 8 children being treated to save one child who has resistant Hib disease. The cost per life saved of such a strategy is K627.20 (K725.20 for 8 courses of ceftriaxone less K98.00 for chloramphenicol). Since no CSF culture facilities exist in most settings where children present with meningitis and since few base hospitals reliably isolate CSF pathogens, treatment based on susceptibility patterns, or even the isolation of specific pathogens, is not currently feasible. Another strategy suggested is to change from chloramphenicol to ceftriaxone if 'the child with meningitis is not responding'. The practical problem with this strategy is that while it may be possible to determine lack of response, it is very difficult to differentiate, using clinical evidence, between poor response due to antibiotic resistance (a minority of cases) and poor outcome due to other factors. A high proportion of children with meningitis due to chloramphenicol-susceptible bacteria, and even those treated with ceftriaxone, have fever for more than 5 days. Other indicators of poor response are the presence of spasticity, neurological deterioration, persistent fits or coma. However, these do not reliably differentiate between children with resistant Hib disease and those with acute sequelae due to other mechanisms, such as cerebral ischaemia, infarction, inflammation and oedema. Moreover even if such acute severe sequelae are due to chloramphenicol-resistant Hib, a change at such a late stage will be unlikely to lead to a favourable outcome. Many children referred with 'poor response to treatment' have sterile CSF; the bacteria have been killed but the brain injury has occurred because of other features of the pathophysiology of meningitis.

Although there are risk factors for resistant gram-negative sepsis (kwashiorkor, adoption, village birth, prolonged hospital stay, and exposure to multiple broad-spectrum antibiotics) the positive predictive values of these are low. Therefore to include ceftriaxone in the Standard Treatment Book for a febrile child with just one of these indications would lead to a large number of children who do not have resistant gram-negative sepsis being treated with ceftriaxone (many false positives). More complicated clinical algorithms might include several risk factors, for example a new fever above 38°C in an adopted malnourished child with severe diarrhoea who has failed to respond to 5 days of first-line standard treatment. Combination indications would increase the positive predictive value of clinical observations, and reduce the unnecessary use of ceftriaxone, but rely on the use of complicated algorithms that are unsuitable for the Standard Treatment Book. These algorithms would still have low specificity in many settings, and would mean that treatment with the right drug would often come too late to be effective. Thus cost, the nonspecific clinical features of antibiotic-resistant infections, and the lack of bacteriology services will prohibit the safe use of third-generation cephalosporins, as well as other higher-generation antibiotics.

The solutions

Where should preventive strategies focus?

Because the total burden of bacterial infections is so great, effective strategies will be those that reduce the use of antibiotics for trivial illnesses, reduce the need to use antibiotics, or decrease the risk factors for resistant bacterial sepsis. Preventive strategies should focus on pneumonia (a huge pool of antibiotic use), meningitis (because as shown above third-generation cephalosporins are neither affordable nor practical for treatment of Hib disease), malnutrition and adoption, low birthweight and septic village deliveries (all of which are risk factors for antibiotic-resistant gram-negative infections). General public health strategies aimed at reducing the prevalence of typhoid in villages and settlements (3,21) may also reduce the prevalence of infection with other enteric pathogens.

Pneumonia and meningitis

In terms of pneumonia prevention to reduce the need to prescribe antibiotics for respiratory

tract disease, strategies should focus on immunization against *S. pneumoniae* and all strains of *H. influenzae*. An affordable pneumococcal vaccine is urgently needed. The conjugate Hib vaccine, although long awaited, is unlikely to reduce the burden of pneumonia greatly, as it has been estimated that only 6-20% of pneumonia cases are due to Hib. In terms of its effect on meningitis, the conjugate Hib vaccine may, however, arrive at just the right time to prevent the overuse of ceftriaxone. Once Hib vaccine is in widespread use, *S. pneumoniae* will predominate as a cause of meningitis and, at least for a time, all pathogens causing meningitis can again be effectively treated with chloramphenicol (as pneumococcal resistance to chloramphenicol is rare). Strict control of use of third-generation cephalosporins is required.

Vaccines against the major pathogens causing pneumonia may be the only truly long-term effective strategies. Before these are introduced more effective outpatient treatment strategies will be important for decreasing bed occupancy. The return of procaine penicillin would reduce the number of pneumonia admissions, and reduce the use of broader-spectrum oral antibiotics. An efficacy trial of oral amoxycillin versus daily procaine penicillin for the treatment of moderate pneumonia is required.

Teaching health workers strategies for avoiding the use of antibiotics for simple cough, but at the same time providing a service that parents view as a satisfactory one, would reduce the pool of unnecessary antibiotic use.

Village maternal health

Village birth is a risk factor for gram-negative sepsis in neonates. Attracting more women to deliver in health facilities where clean midwifery techniques can be practised would have multiple benefits: there would be a lower risk of neonatal sepsis; major obstetric complications would be detected earlier and referred in a timely fashion; and low-birthweight newborns would be referred earlier, rather than waiting for sepsis or dehydration to develop. A prerequisite is for more training in skilled midwifery, mother-friendly labour wards, and clean running water in health facilities. In areas where access is poor, the training of village midwives in clean delivery techniques and neonatal care may be useful. The usefulness of training lay village midwives is controversial (22,23), with some opinion being that only skilled formal midwifery and obstetrics in health facilities will reduce maternal and perinatal mortality. However, there seems little prospect of enough skilled midwives being trained to service all rural areas, or of attracting them and their

TABLE 2

10 BACTERIA THAT EVERY BASE HOSPITAL LABORATORY SHOULD BE ABLE TO CULTURE AND PERFORM SUSCEPTIBILITY TESTING FOR, AND ESTIMATED PERCENTAGE OF ALL CHILD DEATHS

Bacteria	**Estimated percentage of all child deaths**
Streptococcus pneumoniae	7.6-19
Haemophilus influenzae	3.1-20
Pseudomonas aeruginosa	6.2
Klebsiella pneumoniae	5.7
Staphylococcus aureus	4.8
Escherichia coli	4.5
Enterobacter sp	2.8
Streptococcus sp	2
Salmonella typhi	1
Neisseria sp	<1

TABLE 3

11 STEPS TO THE CONTROL OF RESISTANT BACTERIAL INFECTIONS IN PAPUA NEW GUINEA

1 Establish a national antibiotic and antisepsis policy committee (as part of the Pharmacy Advisory Committee) to monitor patterns of antibiotic resistance, antibiotic prescribing and dispensing practices, and sanitation and antisepsis within health facilities; and to develop, implement and assess interventions, such as those suggested below.

2 Strict regulation of commercial pharmacies so that no systemic antibiotics can be sold without a doctor's prescription.

3 Develop bacteriological facilities at all base hospitals, or at all regional hospitals, so that the 10 most important bacteria can be isolated and have susceptibility testing performed.

4 Studies to detect antibiotic-resistant bacteria that result in failure of standard antibiotic treatment, and studies of interventions aimed at preventing them.

5 Introduce *Haemophilus influenzae* type b vaccine, which will eliminate the need to use ceftriaxone for meningitis.

6 A strategy of immunization against pneumococcal disease, which would avoid up to half the prescriptions of antibiotics for pneumonia.

7 An efficacy trial of oral amoxycillin versus daily procaine penicillin for the treatment of moderate pneumonia. Reintroduction of procaine penicillin if found to be more effective.

8 Teaching health workers strategies for avoiding the use of antibiotics for simple cough, while still providing a service that parents view as a satisfactory one.

9 Promotion of hospitals and health centres as places of 'mother-friendly' antenatal care, and as a means of having clean deliveries and healthy (non-infected) babies, and lowering maternal mortality. This requires running water in all health facilities, more skilled midwifery training, and a welcoming attitude by health workers. In remote areas research on the effects of village health workers on total (maternal and neonatal) mortality is required.

10 An education program in hospitals and health centres on interventions that will minimize the risk of nosocomial transmission of infection: promotion of hand-washing, safe injection practices, sterile procedures and ward organization.

11 Public health measures in villages to improve sanitation and control the spread of typhoid.

families to live in remote areas where schools are few and employment opportunities for husbands are limited. There seems little prospect also of attracting a substantially higher proportion of village women to formal perinatal care. In India village-based neonatal care, including the management of sepsis, given by trained village birth attendants reduced perinatal, neonatal and infant mortality (20). Thus there is the chance of a large, but as yet unproven benefit on mortality from extending programs of training lay village midwives. Health research in PNG should measure reductions in total mortality (not reduction in microbial-specific infections) from simple village-based interventions. An example of this could be a controlled trial of the effect of village midwives on maternal and infant mortality. Hard evidence in our setting is needed before time, money and resources are put into what might be an ineffective intervention.

Bacteriological facilities in base hospitals

There is an absolute need to upgrade bacteriological facilities within hospitals. It is only from establishing bacteriological surveillance that an evidence-based approach to antibiotic prescribing can occur. Because there has not been bacterial culture facilities in base hospitals, antibiotic prescribing has commonly been based on expediency, with little thought being given to using narrow-spectrum antibiotics and to the changing patterns of infection and antibiotic susceptibility over time. I suggest that all hospitals should be able to culture and do antibiotic susceptibility testing for the 10 bacteria listed in Table 2. The relative importance of the bacteria is based on their estimated contribution to total mortality in children.

Antibiotic prescribing laws

Strict policing is required of antibiotic prescribing practices by commercial pharmacies and health workers. This is an issue that needs to be addressed by the enforcement of legislation so that no systemic antibiotic can be sold or dispensed by commercial pharmacies without a doctor's prescription.

Conclusions

Resistant bacterial infections are not the biggest child health problem in Papua New Guinea, but they cause substantial mortality. If this problem was approached using the strategies outlined above and summarized in Table 3, not only would resistant bacterial infections be under better control but also, far more importantly, would the major causes of child mortality. Pneumonia prevention using immunization (rather than cure with antibiotics), minimizing the inappropriate use of antibiotics, and extension of antenatal, perinatal and neonatal services to districts to reduce low birthweight and to improve neonatal and maternal survival would concurrently reduce the selection pressure for antibiotic resistance and risk factors for resistant bacterial infections. This emphasizes the interactive nature of the causes of child mortality, and why simple and integrated approaches to reducing child mortality are required.

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