REVIEW

Unnatural selection: reducing antibiotic resistance in neonatal units

D Isaacs

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Antibiotic use selects for antibiotic resistant bacteria. This is an example of rapid Darwinian natural selection in action. It occurs in neonatal intensive care units with the use of parenteral antibiotics, and in the community with oral antibiotic use. A 10 point plan is put forward to reduce antibiotic resistance in neonatal units.

Antibiotic use selects for antibiotic resistant bacteria.¹⁻³ This is an example of rapid Darwinian natural selection in action. It has been shown to occur in neonatal intensive care units with the use of parenteral antibiotics,¹ and in the community with oral antibiotic use.^{2,3} When penicillin was first used in the 1940s and 1950s, *Staphylococcus aureus* was always exquisitely sensitive to benzyl penicillin. Within a very short period of time, most disease-causing strains of *S aureus* were penicillin resistant. The antibiotic pressure exerted by widespread penicillin use had selected naturally occurring mutant strains of *S aureus* that were inherently resistant to penicillin.

Broad spectrum antibiotics might be expected to be more potent selectors of antibiotic resistant bacteria than narrow spectrum antibiotics, and this has indeed proved to be the case in clinical practice.¹⁻⁴ The selection of multiresistant bacteria is causing major problems in neonatal intensive care units. Ampicillin and third generation cephalosporins select for Gram negative bacilli that produce extended spectrum β lactamases, which render the bacterium resistant to many antibiotics, not just β lactams.^{1,5-11} The carbapenems, such as imipenem and meropenem, are used in the laboratory to induce organisms carrying repressed β lactamase genes to express these genes and produce β lactamases.¹² Therefore extensive use of imipenem and meropenem will select for β lactamase-producing organisms, as well as for organisms resistant to imipenem.¹³ Gram positive bacteria can carry genes conferring vancomycin resistance, such as vancomycin resistant enterococci, and genes coding for methicillin resistance, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis*.⁵ Prolonged use of broad spectrum antibiotics is also causing a rising incidence of severe fungal sepsis, even in full term babies, in countries such as India.¹⁴

Antibiotic use selects for antibiotic resistant bacteria, but we still need to use antibiotics to treat babies. The real problem is that prolonged

antibiotic use, particularly with broad spectrum antibiotics, is highly likely to select for highly resistant bacteria. Such excessive use of broad spectrum antibiotics for prolonged periods might be seen as "unnatural selection".

INDUSTRIALISED AND DEVELOPING COUNTRIES

For years neonatologists in industrialised countries in North America, Europe, and Australia have been reporting problems with multiresistant bacteria such as MRSA and Gram negative bacilli that produce extended spectrum β lactamase.^{1,4-9} Similar reports are now appearing from developing countries.^{10,13,14} Two recent reviews of neonatal infections in developing countries have highlighted alarming rates of antibiotic resistance.^{15,16}

We recently surveyed 19 Asian neonatologists, whose names are at the end of this paper, from Malaysia (six), China (four), the Philippines (two), Sri Lanka (two), Thailand (two), and one each from India, Macau, and Mongolia. Seventeen (89%) reported significant problems with sepsis caused by multiresistant Gram negative bacilli, and 16 (84%) reported sepsis due to MRSA. Fifteen (79%) reported high rates of nosocomial sepsis with these organisms. Seven (37%) said that they experienced delay in obtaining microbiology results, while only four (21%) felt unable to rely on the validity of cultures. Nevertheless, there is a strong tendency, at least in India, to start antibiotics without taking blood cultures first, and/or to continue antibiotics if the baby is "sick", even if blood cultures are negative.¹⁴

NEW ANTIBIOTICS

Pharmaceutical companies are understandably keen to promote their antibiotics as "broad spectrum", so that the antibiotics will be used in a wide range of clinical situations where the causative organism is unknown. This is of course a common situation when treating neonates, because the rapidity of infection generally necessitates starting empiric antibiotic therapy without knowing the infecting organism. Being broad spectrum is a double edged sword for an antibiotic. Short term use provides cover against a wide range of organisms, but long term use is a powerful selector for resistance. Imipenem, for example, has activity against a wide range of Gram negative bacilli and Gram positive cocci (except for MRSA), but extensive use of imipenem selects for highly resistant bacteria.¹³

When we have used antibiotics irresponsibly, and babies in our neonatal units are extensively

Correspondence to:
Dr Isaacs, Department of
Allergy, Immunology &
Infectious Diseases,
Children's Hospital at
Westmead, Westmead,
Sydney, 2122, NSW,
Australia; david@chw.
edu.au

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colonised with highly resistant organisms, we may turn to the major pharmaceutical companies and ask why they are not producing new antibiotics. Of course, if a new antibiotic is developed, we do not want organisms to become resistant to it rapidly, so we restrict its use, as severely as we can. It is not surprising that the price of new antibiotics is exorbitant, if we want an antibiotic that will treat the highly resistant organisms we have selected, but then we want to use the new antibiotic as sparingly as possible.

It is unrealistic to expect pharmaceutical companies to solve the problems we have created by excessive and irresponsible use of antibiotics.

RESTRICTING ANTIBIOTIC USE

Which are the best antibiotics to use? It is a fallacy to think that broad spectrum antibiotics are better because they cover more organisms. On the contrary, for that very reason they are more potent at selecting for resistant organisms. In a hugely important study in neonatal units in the Netherlands, de Man *et al*¹⁷ showed that empiric therapy using the “narrow spectrum” antibiotics, penicillin and tobramycin, was significantly less likely to select for resistant organisms than using “broad spectrum” amoxycillin and cefotaxime.

Almost all experts agree that the best empiric regimen for neonates is a penicillin or semisynthetic penicillin together with an aminoglycoside.^{17–21} The choice of the penicillin will depend on the organisms causing sepsis. If it is necessary to cover for staphylococci, then oxacillin, cloxacillin, or flucloxacillin may be most appropriate.¹⁷ In developing countries, it may be necessary to cover for staphylococci from birth, whereas staphylococcal infections are rare in industrialised countries before the third day of age.^{21–22} Empiric vancomycin is not necessary unless MRSA is common,^{17–21} and it is important to restrict vancomycin use in all countries because of the risk of selecting for vancomycin resistant organisms. The choice of aminoglycoside also depends on local data. If the colonising and infecting bacteria in a neonatal unit all become resistant to gentamicin, for example, they may become sensitive again after a prolonged period using an aminoglycoside to which they are sensitive—for example, netilmicin.²²

In some countries, the organisms colonising babies from birth have high rates of antibiotic resistance, suggesting that community antibiotic use has resulted in the mothers being colonised with resistant organisms.¹⁴ The antibiotics of choice for early onset neonatal sepsis will then need to be tailored to cover the likely organisms—for example, it may be necessary to use empiric flucloxacillin and netilmicin for suspected early sepsis if there are high rates of early onset infection with *S aureus* and with gentamicin resistant Gram negative bacilli.

Using antibiotics in rotation has been effective in some settings in reducing resistance.^{23–24} However, most developed countries now place restrictions on which antibiotics may be used and when, and such restrictions have been shown to reduce antibiotic resistance. In a study from Brazil, neonatal unit healthcare associated infections were reduced from 32% to 11% after education and restriction of the use of cephalosporins.²⁵

How does one change antibiotics, if most of the babies on a neonatal unit are already colonised with one or more multiresistant organisms? One way would be to separate (or “cohort”) the babies currently on the unit from any new admissions. The babies colonised with the resistant organisms—for example, MRSA—would be given the appropriate antibiotics (in this case vancomycin with gentamicin) if they developed suspected sepsis. The new admissions would be given flucloxacillin and gentamicin. Provided that the new admissions are protected, by hand washing and good

Ten point plan to reduce antibiotic resistance in neonatal units

- (1) Always take cultures of blood (and perhaps cerebrospinal fluid and/or urine) before starting the infant on antibiotics.
- (2) Use the narrowest spectrum antibiotics possible, almost always a penicillin—for example, benzylpenicillin, flucloxacillin, piperacillin, ticarcillin—and an aminoglycoside—for example, gentamicin, netilmicin, amikacin.
- (3) Do not start treatment, as a general rule, with a third generation cephalosporin—for example, cefotaxime, ceftazidime—or a carbapenem—for example, imipenem, meropenem.
- (4) Develop local and national antibiotic policies to restrict the use of expensive, broad spectrum antibiotics.
- (5) Trust the microbiology laboratory: rely on the blood culture results.
- (6) Do not believe that abnormal results for a non-specific test, such as a raised serum C reactive protein, means that the baby is definitely septic.
- (7) If blood cultures are negative at two to three days, it is almost always safe and appropriate to stop antibiotics.
- (8) Try not to use antibiotics for long periods.
- (9) Treat sepsis, but not colonisation.
- (10) Do your best to prevent nosocomial infection, by reinforcing infection control, particularly hand washing.

hygiene, from the babies colonised with resistant organisms, it should be possible to introduce “narrow spectrum” antibiotics and continue their use once all babies colonised with resistant organisms are discharged.

BLOOD CULTURE RESULTS AND DURATION OF ANTIBIOTICS

It is important that microbiology laboratories use blood culture techniques that are known to be highly sensitive and reliable, such as the BacTec or BacT Alert systems. Once such systems are in place, doctors must rely on blood culture results. Because of the relatively high number of organisms in the bloodstream in neonatal septicaemia, blood cultures are extremely reliable.^{26–27} In a Mexican study of infants, 2.2 ml blood was taken, and divided into 2 ml and 0.2 ml aliquots. If the 2 ml blood culture was positive, the 0.2 ml sample was also positive in 95% of cases.²⁸ It has been shown in industrialised countries that if blood cultures taken for suspected late onset sepsis are negative after 48–72 hours, antibiotics can in general be stopped, and babies do not relapse.^{29–30}

If a baby with suspected sepsis is started on antibiotics, the antibiotics are not being used for prophylaxis but to treat possible sepsis. If cultures are negative two to three days later, antibiotics should almost always be stopped.^{29–30} Exceptions for stopping antibiotics would be where the baby has early or late onset pneumonia, because the sensitivity of blood cultures is only about 50%.³¹ It may also be wise to continue antibiotics despite negative blood cultures in a baby with suspected early onset sepsis, if the baby is heavily colonised with *Listeria* or Group B *Streptococcus* and the mother did not receive intrapartum antibiotics, particularly if a lumbar puncture was not performed.

Prophylactic antibiotics are ineffective in preventing sepsis, whether the antibiotics are given because the baby is intubated, because the baby has an umbilical artery or catheter, a central line, or a chest drain.³¹ If bacteria are

grown from an endotracheal tube culture, that is colonisation unless the baby has pneumonia. The baby should only be treated for pneumonia (on radiograph) or for sepsis, but not for colonisation. Treatment does not reduce colonisation (the endotracheal tube cultures will remain positive) and does not prevent sepsis, but is likely to increase antibiotic resistance.³²

PREVENTION OF NOSOCOMIAL INFECTION

Although it is important that antibiotic use improves, prevention of infection should not be neglected. Simple, cheap but effective strategies are available.^{16 33 34} Improved hand washing has consistently been shown to reduce the incidence of nosocomial sepsis. We all know we should wash our hands, but we could all do better. We are worst at washing our hands when we are busiest. Although this seems logical, unfortunately it is when we are busiest that nosocomial infections are most likely. We should try to wash our hands more, not less, as we get busier. Early introduction of enteral feeds, preferably breast milk, to babies in intensive care allows cannulas to be removed more quickly, reducing the risk of sepsis.³¹

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