Editorial

Neonatal Sepsis: The Antibiotic Crisis

India has an enormous and growing problem of antibiotic use and abuse in newborn care. This is resulting in the selection of increasingly resistant Gram negative and Gram positive bacteria. Gram negative bacteria like Klebsiella can produce extended spectrum beta lactamases (ESBL) which render the Klebsiella resistant to almost all antibiotics(1). Gram positive bacteria can carry genes conferring vancomycin resistance(2), such as vancomycin resistant enterococci (VRE) and genes coding for methicillin resistance, such as methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant *Staphylococcus epidermidis* (MRSE). Prolonged use of broad-spectrum antibiotics is also causing a rising incidence of severe fungal sepsis in India.

Similar problems of antibiotic resistance have been reported in many countries, including both industrialised countries in North America, Europe and Australia(2-6), and in developing countries(7). But it seems that the situation is particularly severe in India, a situation which has reached crisis level.

Background

There is no doubt that excessive antibiotic use selects for antibiotic resistant bacteria. Broad spectrum antibiotics are more potent selectors of antibiotic resistance than narrow spectrum antibiotics. It is known that ampicillin and third generation cephalosporins (cefotaxime, ceftrixone, ceftazidime, *etc*.) select for ESBL producing Gram negative organisms(2-8). The carbapenems, imipenem and meropenem, are used in the laboratory to induce organisms carrying repressed beta lactamase genes to express these genes and produce beta lactamases, so extensive use of imipenem and meropenem will select for beta lactamase producing organisms, as well as for organisms resistant to imipenem.

Furthermore, excessive antibiotic causes neonatal fungal sepsis. Studies have consistently shown that duration of antibiotic use, particularly broad spectrum antibiotics, is the major risk factor for neonatal fungal infection(9-10). Neonatal fungal infection has almost exclusively been described in the very low birth weight (VLBW) baby weighing <1500 g at birth. In general, larger babies are almost never affected unless they require prolonged intravenous feeding, for example because of gut pathology or congenital malformations(11).

Indian Scenario

At the XXIV Annual Meeting of the National Neonatology Forum this year, a number of papers were presented, on the incidence and outcome of sepsis, the organisms causing neonatal sepsis, and their sensitivity to antibiotics. The common themes that emerged from these papers: (*a*) the organisms causing early onset sepsis are very similar to those causing late onset sepsis, (*b*) the commonest organisms causing early and late onset sepsis are Gram negative bacilli, particularly Klebsiella, Enterobactor and *Escherichia coli*. *Staphylococcus aureus* is the commonest Gram positive organism. Group B streptococcus is virtually never isolated, (*c*) there was a high incidence of fungal infection causing late onset sepsis, and anecdotally many of the infected babies weighed >1500g at birth, and some were

even full term.

Most worrying was that there are exceedingly high rates of resistance of Gram negative bacilli to almost all antibiotics. Resistance to aminoglycosides is about 50% for amikacin, higher for netilmicin and over 75% for gentamicin. Resistance to third generation cephalosporins is 80% plus. Bacteria are less resistant (30-46%) to piperacillin-tazobactam. Imipenem resistance is already appearing (about 20%).

It appeared that the major reason for these frightening data were that Doctors often do not take blood cultures before starting antibiotics, if blood cultures are performed and are negative, antibiotics are almost always continued, if the baby remains "sick", more and more potent broad spectrum antibiotics are used, and the belief that a raised serum C-reactive protein (CRP) is proof of sepsis, even if blood cultures are negative.

Evidence Based Antibiotic Use

Unless neonatologists stop using broad spectrum antibiotics for prolonged periods, resistance to antibiotics will rise. Resistance to the carbapenems, imipenem and meropenem, is already appearing in Indian neonates, yet many bacteria are resistant to all other antibiotics. Neonatologists must realise that over-use of broad spectrum antibiotics is irresponsible. The long-term result will be that neonatologists will have no antibiotics left to treat sepsis caused by some organisms. It is no good specialists in tertiary centres continuing to use broad spectrum antibiotics for long periods, while blaming their colleagues in district or private hospitals for misuse of antibiotics which has selected for highly resistant organisms. All doctors must make a combined and concerned effort to improve prescribing practices.

It is important that microbiology laboratories use blood culture techniques which are known to be highly sensitive and reliable, such as the BacTec or BacT Alert systems. Once such systems are in place, as they already are in many laboratories in India, doctors must rely on blood culture results. Because of the high number of organisms in the blood stream in neonatal septicaemia, blood cultures are extremely reliable(12-13). In a Mexican study of infants, 2.2 ml blood was taken, and divided into 2ml and 0.2ml aliquots. If the 2 ml blood culture was positive, the 0.2 ml sample was also positive in 95% of cases14. It has been consistently shown in industrialised countries that if blood cultures are negative after 48 to 72 hours, antibiotics can in general be stopped, and babies do not relapse(15-16). C-reactive protein is a protein produced by the liver, and like other acute phase reactants, including the ESR, will rise following a number of stimuli, including non-infectious inflammation and trauma. In different studies, the positive predictive value of a raised CRP for sepsis has ranged from 6% to 83%(17). In other words, if 100 babies are thought clinically to be septic and have a raised serum CRP, anything between 6 and 83 of them will truly be septic. Antibiotics should not be continued just because of a raised serum CRP. Similarly, thrombocytopenia in the first 3 days of life is rarely due to sepsis. It should not be assumed that the cause of thrombocytopenia is bacterial sepsis, especially early thrombo-cytopenia, which is more likely to have a non-infectious cause. Late-onset thrombocytopenia is more likely to be due to infection, but it should not be assumed to be bacterial infection. Thrombocytopenia is almost invariable in systemic neonatal fungal infection(18), in which case empirically continuing or changing antibiotics will only compound the problem.

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 2-3 days later, antibiotics should be stopped. It has been consistently shown that prophylactic antibiotics are ineffective in preventing sepsis, whether the antibiotics are given because the baby is intubated, because the baby has a central vascular catheter, chest drain or whatever(17). If bacteria are grown from an endotracheal tube culture, that is colonisation. The baby should only be treated for pneumonia (on *X*-ray) or for sepsis, but not for colonisation. Treatment does not reduce colonisation (the ETT cultures will remain positive), does not prevent sepsis, but just increases antibiotic resistance(19).

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, de Man, *et al.*(19-20) showed that empiric therapy with penicillin and tobramycin was significantly less likely to select for resistant organisms in NICUs than amoxycillin and cefotaxime. Almost all experts agree that the best regime is a penicillin or semi-synthetic penicillin together with an aminoglycoside(21-25). 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(21). Vancomycin is not necessary unless MRSA is common(21,25). In India, where Gram negative bacilli predominate, but almost 100% are ampicillin resistant, piperacillin-tazobactam or ticarcillin-clavulanic acid might be appropriate. The choice of aminoglycoside will also depend on local data. If the bacteria all become resistant to say gentamicin, they may become sensitive again after a prolonged period using an aminoglycoside to which they are sensitive, *e.g.*, netilmicin(26). Using antibiotics in rotation has been effective in some settings in reducing resistance(26,27).

Preventing Nosocomial Infection

Although it is important that antibiotic use improves, prevention of infection should not be neglected. Simple, cheap but effective strategies are available(29,30). 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 quicker, reducing the risk of sepsis.

The Future

Neonatologists in India and elsewhere need to use antibiotics responsibly. Indian doctors might be more convinced, if local Indian research could reproduce the data from Oxford and Connecticut showing it is safe to stop antibiotics after 2-3 days if cultures are negative. Here is a simple before-and-after study waiting to be done. The National Neonatal Perinatal Database (NNPD) is collecting wonderful data which will inform whether future changes in practice result in an improvement in resistance patterns. It is important that NNPD continues its excellent work, feeds the results back to neonatologists and monitors any changes in antibiotic resistance. Unless there is a widespread change in practice, antibiotic resistance will continue to be a huge and ever-increasing problem in Indian neonatal units.

It is vital that local and perhaps national guidelines on antibiotic use are developed and implemented in India. These guidelines have

been shown to improve prescribing patterns (27-29). The ten-point plan in the table could probably help in this process.

TABLE-*The Ten Point Plan on Antibiotic Use*

1. Always take cultures of blood (and perhaps CSF and/or urine) before starting antibiotics.
2. Use the narrowest spectrum antibiotics possible, almost always a penicillin (eg, piperacillin-tazobactam) and an aminoglycoside (e.g. amikacin).
3. Do not start treatment, as a general rule, with a third generation cephalosporin (e.g. cefotaxime, ceftazidime) or a carbapenem (e.g. imipenem, meropenem).
4.Develop local and national antibiotic policies to restrict the use of expensive, broad-spectrum antibiotics like imipenem for emergency treatment.
5. Trust the microbiology laboratory: rely on the blood culture results.
6. Stop believing that a raised CRP means the baby is definitely septic.
7. If blood cultures are negative at 2-3 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.

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