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Leading articles

Rationing antibiotic use in neonatal units

Late onset sepsis

In Oxford in 1987 penicillin G and gentamicin were being used to treat babies with suspected early onset sepsis (within 48 hours of birth), and flucloxacillin and gentamicin to treat suspected late onset sepsis.[1] The organisms responsible for early onset sepsis have changed very little since then,[2 3] with group B streptococci and *Escherichia coli* still the major causative organisms, and penicillin G or ampicillin, together with an aminoglycoside, still appropriate empiric treatment for suspected early onset infection.

In contrast, the organisms responsible for late sepsis have changed. The most commonly isolated organisms from babies with late onset sepsis, responsible for 50% or more episodes of systemic sepsis in Australia,[4] the USA,[5] Britain[6] and many other countries, are now coagulase negative staphylococci. Most of these—over 90% of those cultured in Australia—are methicillin resistant.[4] Only half of the isolates of coagulase negative staphylococci in Australia are associated with the presence of a central silastic intravascular cannula.[4]

Vancomycin and vancomycin resistant organisms

As a result of the increase in staphylococcal infections, many neonatal units in Australia and the United Kingdom use vancomycin as part of their first line empiric treatment for suspected late onset sepsis. Vancomycin is a glycopeptide antibiotic, originally introduced in the 1960s, which lost favour because of perceived toxicity, but was re-introduced because it is active against methicillin resistant strains of *Staphylococcus aureus* (MRSA) and coagulase negative staphylococci. Vancomycin is active against most Gram positive organisms, but not against Gram negative organisms or anaerobes.

The emergence of Gram positive organisms which are resistant to vancomycin, and for which there is no effective antibiotic, is of deep concern. The first were the vancomycin resistant enterococci (VRE),[7] but the emergence of strains of vancomycin insensitive *Staphylococcus aureus* (VISA) is even more worrying. Many countries have introduced guidelines so that hospitals restrict the use of vancomycin to an absolute minimum.[8] In neonatal units where MRSA is endemic, it is impossible not to use vancomycin as first line empiric treatment for suspected late onset sepsis. Selection of vancomycin resistant strains is most likely to be avoided if the vancomycin is stopped after two to three days when systemic cultures are negative. Some units with no MRSA colonisation use vancomycin as first line treatment because of methicillin resistant coagulase negative staphylococci. However, this risks selecting vancomycin resistant organisms for which there will be no effective treatment. Similarly, the use of continuous infusions of low dose vancomycin is highly likely to select for vancomycin resistant organisms.

Flucloxacillin

A lesser evil may be to use flucloxacillin and an aminoglycoside as first line treatment, and only switch to vancomycin if coagulase negative staphylococci (or Gram positive cocci) are growing in blood cultures. The mortality from coagulase negative staphylococcal sepsis is low. In a recent Australian series, two of 124 babies with sepsis caused by coagulase negative negative staphylococci died, possibly but not definitely due to sepsis,[4] while in an American multicentre study of very low birthweight babies, the eventual mortality was 10% in babies with coagulase negative staphylococcus sepsis and 7% in babies who never became septic.[5] Coagulase negative staphylococci very rarely cause fulminant sepsis, so there is almost always time to change to vancomycin when cultures are positive. Aminoglycosides have some anti-staphylococcal activity, which may help limit the severity of infection.

Aminoglycosides

Aminoglycosides are cheap and effective. However, there is a problem with resistance. Aminoglycoside resistant Gram negative bacilli have caused outbreaks,[9 10] including those due to organisms with plasmid mediated resistance to multiple organisms. Such outbreaks continue to occur.[11] Aminoglycoside resistant organisms are thought to be selected by high level use of antibiotics, but spread of resistant organisms to other babies occurs with increased workload,[12] and is thus preventable by improved handwashing. Secondly, aminoglycosides penetrate uninflamed meninges poorly, in contrast to third generation cephalosporins, and this has been used as a rationale for using cephalosporins in preference to aminoglycosides. An alternative would be to perform a lumbar puncture on any baby with suspected late onset sepsis to exclude meningitis.[13] If the cerebrospinal fluid is normal, the relative penetration of

Table 1 Recommended antibiotic regimens for empiric treatment of suspected late onset sepsis (with normal CSF)

Situation	*Antibiotic regimen*
No MRSA on unit	Flucloxacillin and gentamicin
Risk of MRSA	Vancomycin and gentamicin
ESBL outbreak	Imipenem or meropenem

aminoglycosides and cephalosporins becomes irrelevant. A third argument for not using aminoglycosides is the cost of measuring aminoglycoside concentrations.

However, about 90% of episodes of suspected late onset sepsis prove negative, and it is safe to stop antibiotics after 2–3 days without measuring drug concentrations, if systemic cultures are negative.[14] Thus it should only rarely be necessary to measure serum aminoglycoside concentrations.

Third generation cephalosporins

Because of the real or perceived problems with aminoglycosides, many neonatal units have elected to use third generation cephalosporins for empirical treatment of suspected late onset sepsis. Third generation cephalosporins are broad spectrum antibiotics, active against most Gram negative and many Gram positive organisms. Broad spectrum activity is presented as a virtue by drug companies and perceived as such by many clinicians. However, its use, and particularly prolonged use, is associated with fungal infections,[15] and may in part, explain the rising incidence of systemic candidiasis in neonatal units.[16] Its use is also associated with the selection of cephalosporin resistant Gram negative bacilli.[17] Furthermore, in 1983 extended spectrum beta lactamase (ESBL) producing strains of Gram negative bacteria were first reported from Germany, apparently selected by excessive use of third generation cephalosporins.[18 19] These organisms carry a plasmid mediated beta lactamase which confers not only resistance to cephalosporins, but also resistance to most aminoglycosides and many other antibiotics. Some ESBL strains are sensitive to amikacin, but many are sensitive only to the new carbapenems, imipenem and meropenem.

Which antibiotics to use?

Flucloxacillin and an aminoglycoside, such as gentamicin, are thus arguably the best choice for initial empiric treatment for suspected late sepsis, in the absence of endemic MRSA colonisation of babies, and when the baby's cerebrospinal fluid is normal (table 1). Empiric treatment with third generation cephalosporins can be used during an outbreak,[20] or when indicated by an abnormal cerebrospinal fluid. When severe coagulase negative staphylococcal sepsis seems highly likely—for example, in a severely ill baby aged 5–14 days with a silastic cannula in situ and perhaps with thrombocytopenia[4]—empiric treatment with vancomycin might be advisable. Imipenem should be reserved for ESBL outbreaks.[20] Some recommended antibiotic regimens for late onset sepsis are shown in table 1.

Reducing the duration of antibiotic use is extremely important. Colonisation with Gram negative bacilli increases greatly when antibiotics are continued for more than 3 days.[21] If systemic cultures are negative, antibiotics can safely be stopped after 2 to 3 days, and babies do not relapse from missed sepsis.[14]

In many neonatal units antibiotics are prescribed because an organism is cultured from an endotracheal tube aspirate. If the baby does not have pneumonia, then this is treating colonisation, not disease. In a study of babies with late onset pneumonia, potential pathogens could be cultured as frequently from endotracheal tubes of ventilated control babies without pneumonia as from those babies with pneumonia.[22]

Another common practice is to start babies on antibiotics because of the presence of an invasive device such as an umbilical arterial or venous catheter, intercostal drain, or even endotracheal tube. Such use of prophylactic antibiotics does not prevent sepsis,[23] and the only likely outcome is to select for multiresistant organisms.

Conclusions

- Rational antibiotic use involves rationing antibiotic use.
- Use narrow spectrum antibiotics whenever possible.
- Keep potent broad spectrum antibiotics in reserve.
- Stop antibiotics early, after 2 to 3 days, if systemic cultures are negative.
- Treat sepsis, not colonisation.
- Do not use prophylactic antibiotics without evidence of their efficacy.

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