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Review Article

Appropriate use of antibiotics in the NICU

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Abstract. Antibiotics are a very important group of drugs for the sick neonate and have undoubtedly played a role in their improved survival. But they come with a set of risks which must be carefully considered and weighed against the benefits in any decision to commence antibiotics. For the neonatologist this is not an easy task. This article intends to discuss the potential risks of antibiotics to the sick newborn in the hope that it will aid clinicians to better balance the benefits and harms and use antibiotics in a rational way.

Key words: Neonates, antibiotics, policy, infection, sepsis

1. Introduction

Antibiotics are the commonest drugs used in the NICU. Virtually all extremely low birth weight infants receive antibiotics and for all other birth weight groups admitted to the NICU the vast majority are treated with antibiotics (1, 2). However of those who receive antibiotics only a small number eventually have culture proven infection. Clark et al reported that 98% of preterm infants who received empiric antibiotics were culture negative (1). The neonatologist needs the skills and knowledge to weigh the benefits and harms of antibiotics. This would best be done on each individual baby. Most neonatal units have policies on antibiotic use. Are these policies helpful or are they constraining us to use antibiotics appropriately? The purpose of this article is to review our current understanding on the risks and benefits of antibiotics and suggest how best to balance the benefits and harms when using antibiotics in the NICU.

2. Defining infection

Neonatal infection has been classified as early and late onset infection. Early onset sepsis (EOS) is present at birth or presents within the first 48 hours of life. It is mainly caused by vaginal or perineal organisms. The most common infecting organisms are Group B Streptococcus (GBS) and *E coli* but can include a wide variety of organisms. EOS will commonly present as a respiratory illness which is not easily distinguishable from other respiratory conditions or it may present as a generalised infection and occasionally as meningitis.

Late onset sepsis (LOS) presents after 48-72 hours of life. It can be hospital or community acquired and sometimes may also be due to perinatally acquired organisms. The organisms responsible are from the infants environment and the people in it be it a hospital or the home. The organisms causing hospital acquired infection in the NICU depend on the prevailing organisms present in the unit and vary from one unit to another. Nosocomial infections in NICUs in both developed and developing countries are most commonly due to coagulase-negative *Staphylococcus aureus* (CONS) (3). LOS may cause respiratory disease, generalised infection, meningitis or focal infections such as septic arthritis and urinary tract infection.

3. Defining antibiotic treatment

It is convenient to classify the use of antibiotics into three main strategies, 1) prophylaxis 2) empirical treatment and 3) definitive treatment.

3. 1. Prophylactic antibiotics

Prophylactic use of antibiotics implies that they are given to prevent infection. Prophylactic antibiotics are not indicated in almost all situations in neonatology. There is high level evidence to show that they are not useful for the prevention of infection following umbilical vessel or central venous catheterisation (4-6). Three randomised controlled trials looking at antibiotics in infants with meconium aspiration syndrome in

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nearly 500 patients have all failed to show a benefit (7-9). Until evidence of benefit comes to light we should not use antibiotics in meconium aspiration syndrome except perhaps for those with risk factors of infection. Similarly there has been a practice to start antibiotics for all infants receiving mechanical ventilation. This practice is again not supported by evidence from randomised controlled trials (10).

The only prophylactic use of antimicrobials that may be justified is the use of fungal prophylaxis in preterm infants on broad spectrum antibiotics, or with central arterial or venous lines. A Cochrane systematic review suggests oral or topical antifungals reduce the incidence of systemic fungal infections (11). Further information on the safety of their use is needed. To date there is no evidence that use of oral prophylactic antifungal agents has changed the susceptibility of infecting organisms (12).

3. 2. Empirical antibiotics

Empirical antibiotics are used when infection is suspected. Infection could be just one of several explanations for an infant's illness so we 'cover' with antibiotics. A common setting is to start antibiotics in all neonates with respiratory distress, in particular those who have risk factors for infection such as maternal chorioamnionitis and pre-labour preterm rupture of membranes. This stems from the idea that it is difficult to distinguish infection from other causes of respiratory distress and indeed they may coexist.

3. 3. Treatment antibiotics

Sometimes we are sure that an infant has clinical or proven infection and we make a decision to treat the infant with a full course of antibiotics.

4. Reasons for restricting antibiotic use in the NICU

4. 1. Effect of antibiotics on the neonate

The newborn infant is born with a sterile gut. The normal flora becomes established over the early days of life. Antibiotics are one of the main factors influencing the development of the intestinal microflora. Antibiotics were associated with a delay in microflora colonisation with most anaerobes, importantly *Bifidobacterium* and *Lactobacillus*. At 30 days of life *Bifidobacterium* and *Lactobacillus* s*p* were only identified in one of 15 breastfed preterm infants who had received antibiotics. This is in contrast to it being the predominant organisms in the flora of term breastfed infants who have not received antibiotics. Antibiotics also limit the number of bacterial species in the normal flora (13-19). Most extremely low birth infants had as few as 3 species in their flora at Day 10 of life and there was an inverse dose-response between the duration of antibiotics and the number of species in the flora at Day 30 of life (19). Lack of these organisms was related to bacterial overgrowth of other species. We can conclude that antibiotics play a major role in restricting the diversity and the volume of the normal flora thus reducing protection from invading pathogens.

Animal studies have suggested that normal gut development is dependent on a diverse and high volume flora and the normal flora also plays a significant role in the physiological and immunodevelopment of the gut (20, 21). Not only does the normal flora create a physical defence but it also plays a role in immune responses. For example it has been shown that a polysaccarhide produced by *Bacteroides fragilis* plays a role in directing the cellular and physical maturation of the gut. *Bifidobacterium* has been shown to play a role in immunomodulation. It helps balance pro-inflammatory and anti-inflammatory cytokine production in the gut resulting in a net anti-inflammatory response (22). It has been postulated that the low bacterial counts and lack of diversity of anaerobes caused by antibiotic use may have a role in the pathogenesis of necrotising enterocolitis (NEC). One study that supports this was a large study of 5783 extremely low birth weight infants from 19 centres who received empiric antibiotics at birth. Of those who were subsequently found to be culture negative at birth there was an association between NEC and prolonged use of empiric antibiotics for greater than 5 days. For every additional day of empiric antibiotics the risk of NEC increased (2).

4. 2. Resistance and antibiotics

Antibiotics alter the gut flora resulting in colonisation with resistant organisms. They serve as a reservoir and this resistance is subsequently passed on to pathogenic organisms. Such resistance is usually to multiple drugs. Infections caused by multi-resistant organisms have a higher mortality (12). There is evidence that some antibiotics may be more likely to cause this than others.

This was studied in two identical NICUs. One NICU was assigned an empiric antibiotic regime of tobramycin and penicillin for EOS and tobramycin and flucloxacillin for LOS and the second unit was assigned cefotaxime and ampicillin. After 6 months the regimes were reversed. Respiratory and rectal cultures were

taken weekly. Over 218 admissions in each unit, the relative risk of colonisation with resistant strains was 18 with the cefotaxime and ampicillin regime and this reversed when the regimes were reversed. There were no cases of EOS in either group. Four LOS occurred during the study period, 3 in the cefotaxime and ampicillin group and one in the other group (23). Thus antibiotic policies do influence the type of organism colonising infants in a NICU. A regime with beta-lactam antibiotics is more likely to cause colonisation with multiresistant organisms and regimes that restrict the use of beta-lactam antibiotics reduce resistance. Use of aminoglycosides was not associated with significant emergence of resistant organisms. Another concern for cefotaxime has been its association with increased mortality. This was found in a retrospective study of over 100,000 infants given either gentamicin or cefotaxime with ampicillin empirically in the first 3 days of life. The relative risk of mortality was increased 1.5 times for infants receiving cefotaxime. The authors performed logistic regression analysis to adjust for other predictors of mortality as well as adjusting for the site of care and antibiotic choice. Similar data has suggested that cefotaxime use may increase the risk of fungal infection (24).

5. How to restrict antibiotic use

5. 1. Stopping antibiotics early in EOS

Stopping empiric antibiotics in the absence of infection is now widely practiced. The first requirement for such a practice is to do a blood culture before starting antibiotics. Antibiotics would be started in the preterm infant for a variety of risk factors but would generally not be started in the term infant except in the context of maternal clinical chorioamnionitis (25). Antibiotics would then be stopped early in the context of a negative blood culture and other indices of infection not suggestive of infection. The incubation time to positive culture varies by organism. Organisms responsible for EOS are usually positive after culture for 36 hours while organisms causing LOS are positive by 48 hours. This means that if no growth is present by these times and there is no other evidence of infection that antibiotics can safely be stopped (26). If automated blood culture systems are not used the time to positivity may be slightly longer (26, 27).

There is a lot written about the diagnosis of infection and unfortunately it is still not a straight forward task. Unfortunately clinical features have failed to be useful. Those that might indicate infection include temperature instability, respiratory distress, circulatory disturbance and hepatosplenomegaly. However these are equally likely to be present in other serious conditions around birth such as perinatal asphyxia, and acute blood loss such as that seen in fetomaternal haemorrhage. Investigation may or may not be helpful. Current investigations lack the sensitivity and specificity needed to confidently diagnose infection. Blood culture and absolute neutrophil count are the most widely available tests and on their own are somewhat useful. Immature to total neutrophil ratio and C-reactive protein are also fairly widely available and add value to the above. Some have used scoring systems involving multiple parameters (28). More recently interleukin-6 and procalcitonin have been shown to be helpful (29, 30). The lack of reliable sensitive and specific diagnostic tests for sepsis is probably the most important reason for overuse of antibiotics.

So in making a decision to discontinue antibiotics we are left with making a clinical judgement. We have to weigh up the clinical condition with the blood culture and other available supporting investigations as well as considering the benefits and risks to the baby in continuing empiric antibiotics when infection is not present. This is by no means a straightforward task.

5. 2. Restricting antibiotic use in LOS

The choice of antibiotics for late onset infection would depend on the resident flora in the neonatal unit. As mentioned above the antibiotics used in the unit does have some bearing on the organisms present in the unit but there are other factors too.

In most units CONS is the commonest infecting organism followed by *Klebsiella*. This pattern is seen in well resourced settings as well as in less resourced settings in Asia (3, 31). CONS is frequently resistant to methicillin. Suitable antibiotics might be an aminoglycoside such as gentamicin and vancomycin. A problem with gentamicin is that it has poor CSF penetration when the meninges are inflamed. This means that lumbar puncture would need to be considered in every LOS to exclude meningitis.

One of the main concerns about using vancomycin is that it will encourage vancomycin resistance. Indeed there are now more than a few reports of vancomycin resistance *Enterococcus* infection (32, 33).

Main Messages (Box Table)

How to restrict antibiotic usage
• Don't use prophylactic antibiotics
• Consider carefully whether antibiotics are needed
• Avoid broad spectrum antibiotics
• Avoid cefotaxime and other beta-lactam drugs
• Always do a blood culture
• Obtain blood culture report at 36-48 hours
• Shorten duration of treatment
• Stop antibiotics when no infection evident at 36-48 hours
• Treat LOS for gram negative infections and wherever possible wait for culture before treating gram positive infections

Therefore it is important to limit its use as much as possible. Gram negative infection is more fulminant than gram positive infection and it has been suggested that it may be possible to start treatment for gram negative infections and wait for blood culture reports before adding vancomycin to treat CONS (34).

6. Gentamicin nephrotoxicity and ototoxicity

6. 1. Is this an important reason for restricting use of gentamicin?

Toxicity is a frequent concern for patients on aminoglycosides. This is caused by the uptake of aminoglycosides to the brush border of the nephrocyte and the cochlear and vestibular membranes (35). It has been shown that this is more likely to occur when drug levels are sustained compared with high intermittent exposure (36). Current regimes make use of a high peak and low trough that result in no sustained exposure of the kidney or ear to the drug minimising the possibility of toxicity. Gentamicin is given once daily or perhaps even less frequently. The sick preterm often has a low glomerular filtration rate. The current once daily or longer dosing interval gives a longer duration for excretion of a dose thus reducing the possibility of accumulation of the drug.

There are many reasons for a high creatinine level in the sick neonate including low fluid intake, low renal perfusion, and high fluid losses particularly high insensible water loss. This means that renal function tests are not a useful marker of toxicity in the sick newborn. High creatinine levels are not an indication for stopping gentamicin. If a baby requires gentamicin for more than 48 – 72 hours peak and trough levels should be done and in the presence of reduced renal function dose quantum or dose interval modification may be necessary.

With the current once daily dosing regime there is little evidence of either nephro-or ototoxicity in the newborn. In fact evidence suggests that the neonate is relatively less at risk of ototoxicity than the adult (37). Fear of nephro- or ototoxicity would only seldom be a consideration in restricting the use of aminoglycosides.

7. Conclusion

There are important reasons for weighing up the benefits and harms of antibiotics. There are many reasons why neonatologists would want to start empiric antibiotic treatment. These reasons include, the immature immune system, the lack of specific clinical features for infection and the use of multiple invasive procedures. This article presents a number of reasons why antibiotic use should be restricted as much as possible without compromising the safety of the patient. This is a source of direct conflict for the neonatologist. There is a need to avoid the effects of antibiotics on the growth and development of the neonatal intestinal tract and immune system as well as avoid breeding resistance organisms in the NICU milieu. A policy of restriction of antibiotic usage is important. Careful choice of antibiotics can also help reduce transmission of antibiotic resistance in the NICU. Further research into strategies of further restricting antibiotic usage without compromising care is needed.

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