Original Article

Is 24 hour observation in hospital after stopping intravenous antibiotics in neonates justified?

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Abstract

Background: Antibiotics are given empirically for suspected sepsis in up to 75% of neonates on the Neonatal and Paediatric Intensive Care Unit (NPICU), after completion of a septic screen. Treatment is discontinued on day 3 if cultures remain negative or after 7-14 days with proven sepsis and, until recently, these neonates are then observed for an additional period of 24 hours before being discharged from hospital.

Aim: To assess whether the 24 hour observation period after stopping antibiotics is clinically justified and, if not, whether neonates can be discharged safely on the same day when antibiotics are stopped.

Methods: A consecutive sample of 95 babies admitted to NPICU, and who received antibiotics, from December 2006 to January 2008 were analysed prospectively. Their clinical presentation, predisposing risk factors for neonatal sepsis, investigations, antibiotic details and medical management including respiratory support were recorded, and correlated with all events that may have occurred during the observation period after stopping antibiotics.

Results: No adverse events were documented in the 24 hour period after antibiotics in all 95 neonates in this study and, therefore, there was no association with any potential predisposing risk factors.

Conclusion: The need to observe neonates for a period prior to discharge after stopping antibiotics is not supported on clinical grounds and, as a result of this study, has been discontinued. Neonates can be discharged from hospital safely and immediately on stopping antibiotics, thus reducing hospital stay and an estimated cost saving of approximately €18,000 to the service provider per annum.

Keywords

Antibiotics, neonates, hospital observation

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Introduction

Neonatal sepsis is classified into early onset (infection occurring in the first 5 days of life) and late onset (after 5 days of age).[1,2] Early and late bacterial sepsis in the neonatal period often involve different micro-organisms but both can be a major cause of morbidity and, if untreated, carry a mortality of 50%.[3] The presentation of neonatal sepsis is often non-specific,[4] although acute onset with rapid, often catastrophic clinical deterioration is common, especially in preterm infants and those with very low birthweight (<1500g).[5] Commonly isolated organisms include coagulase negative staphylococci, *Staphylococcus aureus, Streptococcus agalactiae* and *Escherichia coli.*

In contrast to the approach in older children, neonates are presumed septic with minimal clinical suspicion.[4] Consequently, up to 75% of all neonates admitted to NPICU, Mater Dei Hospital, Malta, undergo at least one septic screen, usually including blood and cerebrospinal fluid cultures,[6] immediately followed by empiric broad spectrum antibiotics designed to cover the more common organisms.[7-9] Based on the prevailing infecting organisms on our NPICU, benzylpenicillin and cefuroxime are administered as empiric 'first line' antibiotics, whereas co-amoxiclav and cefotaxime empirical 'second line' antibiotics if meningitis is suspected and meropenem and teicoplanin as 'third line' if there is no apparent response to the above antibiotics. Although a bacterial cause is confirmed in less than 10% of these infants, antibiotics are continued for at least 72 hours until cultures and indicators of sepsis (e.g. C-reactive protein: CRP)[6] are reported to be negative. Confirmed sepsis necessitates a 7-14 day course of appropriate antibiotics, according to the organism and site of infection.[7]

Until recently, it was Unit practice for neonates to be observed in hospital for a further 24 hours once antibiotics

were discontinued, regardless of whether these were started empirically or following positive cultures. This antibiotic-free period was observed even though there were no indicators of sepsis. However, although this policy was written into the antibiotic-sepsis protocol for the Unit, it was not evidence-based and this study was designed to evaluate whether it is clinically justified and, therefore, whether the practice could be stopped safely.

Methods

All neonates aged >32 completed weeks gestation admitted to the NPICU and who were started on antibiotics for suspected or proven sepsis from December 2006 to January 2008 were analysed prospectively. For all cases, data related to the immediate antenatal history, the infant, investigations and management were documented (Table 1). Adverse events were defined as any events that occurred after stopping antibiotics during the 24 hour 'observation period' and, if adverse events did occur, all details relating to these events were documented. This study set out to determine whether there was any relationship between any patient data and discontinuing antibiotic therapy and any observed adverse effects thereafter.

Premature infants aged <32 weeks gestation were excluded from the study because, in this group, factors other than antibiotic therapy (with or without an observation period after stopping antibiotics), determine the time of discharge from hospital (e.g. attainment of a gestational age of ≥35 weeks and weight ≥2000g). Furthermore, once off all therapeutic treatment, it is unit practice to encourage these babies to 'room in' with their parents for between 1-3 nights prior to discharge. Chi squared was applied to compare the association of any adverse events during the observation period, taking $p \leq 0.05$ to be statistically significant.

Table 1: *Data collected relating to patients, investigations and management*

General data
Maternal health during pregnancy, time of rupture of membranes before delivery

Infant data
Date of birth, gender, gestation, birth weight, mode of delivery, Apgar score at 1 and 5 minutes
age at admission to NPICU, temperature on admission, symptoms and signs on admission

Investigations
White cell, neutrophil and platelet counts, sequential CRPs, blood, urine and CSF cultures, chest X-ray

Management
Type of central line, mode and duration of respiratory support (if any), any other support (e.g. inotropes)
type and duration (in days) of antibiotics

Results

During the study period, a cohort of 95 cases out of 297 admissions to the NPICU fulfilled the entry criteria. Of these, 69 were males and 26 females with a gestation of 32 to 43 completed weeks (mean 34.75 weeks, median 38 weeks), and birth weight of 1.51 - 4.75kg (mean 2.97kg, median 2.95kg, SD 0.64). As shown in Table 2, predisposing risk factors present in the mothers, duration of ruptured membranes and mode of delivery were not associated with any adverse effects on stopping antibiotics. Similarly, no parameter relating to the infant's gestation, birth weight, Apgar score and clinical condition requiring admission, investigations and management was observed to be associated with any adverse events after stopping antibiotics.

On admission to NPICU, empirical first line benzylpenicillin and cefuroxime were administered in 70 (74%) cases, co-amoxiclav and cefotaxime (empirical second line antibiotic) in 21 (22%) cases, and 4 others received different antimicrobials according to sensitivities. One infant included in this group also received acyclovir for 14 days for suspected herpes infection. First line antibiotic cover was subsequently changed to second line in 6 infants and changed to third line antibiotics (meropenem and teicoplanin) in 1 infant, following a rise in CRP, growth in blood cultures or deterioration in the clinical condition.

The duration of antibiotic treatment ranged from 2 to 14 days (mean 4.9 days, median 5 days, SD2.2). In 24 (25%) and 53 (56%) cases, antibiotics were stopped after 72 and 120 hours, respectively, as serial CRPs and blood cultures remained negative. Eighteen cases required antibiotics for longer periods, ranging from 7-14 days, due to confirmed or strongly suspected sepsis.

Of the 95 infants who received antibiotics, 26 (27%) infants did not require any respiratory support, 13 (14%) needed oxygen via nasal prongs, 52 (55%) had nasal continuous positive airway pressure (CPAP) and 4 (4%) cases required intermittent positive pressure ventilation.

Adverse events

After stopping antibiotics and prior to discharge from hospital, neonates were observed without treatment on the NPICU (52 cases) or postnatal ward (43 cases) for periods of observation ranging from 0.5-13 days (mean 1.8 days, median 1 day, SD 2.2). The majority (73) were observed for 24 hours before discharge. The length of observation was longer in 22 others due to other factors including prematurity, inadequate weight gain and feeding difficulties.

No adverse events were recorded after stopping antibiotics in any of the 95 neonates studied, including those who had had a difficult neonatal course requiring ventilation and prolonged courses of antibiotics because of documented sepsis (Table 2).

Discussion

Although several neonates are investigated for sepsis, only 3–8% will be found to have culture-proven infection, translating into an incidence of just 2 in 1,000 live births.[1,7] However, since

the early signs of sepsis in the newborn are often non-specific [4] and the consequences of untreated sepsis are often dire,[3] many newborns undergo diagnostic 'septic screens' and the initiation of antibiotic treatment empirically, and certainly before the diagnosis can be determined on culture.[7-9] In our unit, this practice is carried out in 75% of admissions to NPICU.

The risk factors for neonatal bacterial sepsis as listed in Table 3 are well documented.[1,5,7] Many of these risk factors are common and, therefore, empiric antibiotic use in neonates is justified.[7-9] Equally important, however, is the discontinuation of these antibiotics as soon as possible if sepsis is not confirmed and, therefore, they are no longer required. Indeed, prolongation

Table 2: *Association between cohort characteristics and risk factors with observed adverse effects*

Documented parameter	*Details*	*Association with adverse effects*
Cohort (n=95)	• 69 male; 26 female • gestation 32 to 43 completed weeks (mean 34.75, median 38 weeks) • birth weight: 1.51 - 4.75kg (mean 2.97kg, median 2.95kg, SD 0.64)	None
Mothers (n=95)	• 5 group B streptococcal (GBS) colonisation; 4 fever during delivery; 2 foul smelling liquor (but culture negative); 1 genital herpes; 1 rubella seroconversion during pregnancy; 1 parvovirus infection	None
Rupture membranes	• 0 (elective LSCS) to 216 hours (mean 7.1hr, median 1.5hr, SD 24) • four cases had prolonged rupture of membranes > 24 hours	None
Delivery	• 33 born vaginally, 5 ventouse, 25 elective LSCS, 32 emergency LSCS • 82 had Apgar scores ≥7 at 1 & 5 minutes; 13 had score ≤6 at 1 or 5 min	None
Admission NPICU	• age at admission: 0.5 hours to 6 days (mean 8.5hr, median 2hr, SD 20) • 62 babies normothermic, 30 hypothermic (<36.5°C), 3 febrile (>37.5°C) • 68 (72%) respiratory distress; 9 (10%) with cyanosis, 6 vomiting and feeding problems, 5 omphalitis, 3 fever, 1 convulsions	None
Investigations	• total white cell range: 4.7-34.6x10^9/l with 19 cases abnormally raised • neutrophils: 1.5-17.8x10^9/l with 10 cases having an abnormal count[1] • 8 thrombocytopenia below <150 x 10^9/l • CRP was positive (>10) in 11 cases (range 14-181)	None
Microbiology	• Positive blood cultures in 12 cases but only 2 with *Serratia marcescens* and *Staphylococcus aureus* had raised CRP; other pathogens included 5 *Staphylococcus albus**, 3 *Enterococcus faecalis*, 1 *Moraxella osteolensis,* 1 *Group B Streptococcus* (*NB: blood cultures collected by open drip method accounting for number of presumed contaminants) • CSF and urine cultures in 8 cases were all negative • chest X ray showed increased hilar markings in 30 from total 90 cases, confirmed to be within normal limits by reporting radiologists	None
Management	• 24 (25%) had indwelling central catheters (18 umbilical arterial, 5 umbilical venous, 2 radial arterial lines and 1 femoral venous line) • benzylpenicillin + cefuroxime administered in 70 (74%) cases; co-amoxyclav + cefotaxime in 21 (22%) cases; 4 others received different antimicrobials according to sensitivities • 1 infant included received acyclovir for 14 days for suspected herpes • 6 infants received further antibiotics (meropenem + teicoplanin) following a rise in CRP, growth in blood cultures or deterioration in the clinical condition • antibiotic duration 2 to 14 days (mean 4.9 days, median 5 days, SD2.2); in 24 and 53 cases, antibiotics stopped after 72, 120 hours, respectively. 18 required antibiotics for 7-14 days, due to confirmed sepsis • 26 infants needed no respiratory support, 13 nasal prong oxygen, 52 nasal CPAP, 4 cases required intermittent positive pressure ventilation	None

Legend: SD=standard deviation; LSCS=lower segment caesarian section; CRP=C reactive protein; CPAP=continuous positive airway pressure

Table 3: *Risk factors for bacterial sepsis in neonates*

Newborn risks	*Maternal risks*	*Others*
Prematurity	Premature rupture membranes	Poor antenatal care
Very low birth weight (<1000g)	Prolonged rupture membranes	Poor maternal nutrition
Male>female	Maternal GBS	Substance abuse
Low Apgar score (<6 at 1 & 5min)	Maternal fever >38.4°C	
Perinatal asphyxia	Chorioamnionitis	
Meconium staining	Urinary infection	
Congenital anomalies		

Legend: GBS=Group B streptococcus

of unnecessary antibiotics has been shown to be associated with, for example, greatly increased colonisation with gram negative bacilli when antibiotics are continued for more than 3 days.[10] Similarly, prophylactic antibiotic use to cover an invasive device such as an intercostal drain, umbilical arterial or venous catheter, does not prevent sepsis and is only likely to select for multi-resistant organisms.[11,12] Hence, if systemic cultures are negative, antibiotics should be stopped after 48 hours. This is usually possible, particularly if automated blood culturing systems are used, but delays of up to 5 days for a final culture result are observed where this system is not established, resulting in lengthier administration of empiric antibiotics. Indeed, cessation of antibiotics at the earliest opportunity is widely established and has not been shown to be associated with a recurrence or the emergence of breakthrough sepsis.[7] However, the additional 'safety measure' adopted by our Unit for a further period of observation in hospital for potential adverse effects is not evidence-based. Despite the study's limitations in a lack of a control group and failure to blind the authors to the treatment the infants' received, this study did not report any adverse effects during the precautionary period of observation. Indeed, this study analysed several known risk factors, itemised above, that may have resulted in complications after stopping antibiotics: yet, in all the cases, no events were recorded in the 24 hour period of observation, regardless of gender, weight, mode of delivery, Apgar score, respiratory support, documented or suspected sepsis, days and type of antibiotics received.

Conclusion

This study therefore challenges the current practice for a period of pre-discharge observation, and strongly supports the practice whereby neonates with a mean age of 38 weeks and without other confounding problems, can be safely discharged home on the same day as stopping antibiotics. As a result of this study, the discontinuation of this unnecessary practice would have reduced the average stay in hospital for 73 out of the total of 95 infants in the study cohort by 24 hours. This translates into a cost saving on hospital stay of approximately €18,000 (including bed stay and consumables) for this group of patients and, in turn, a similar recurrent saving for the unit each year. Clearly, earlier discharge would also minimise anxiety and inconvenience to the family and, for all these reasons, the 24 hour precautionary observation period has now been discontinued.

References

1. Rennie JM. Infections in the newborn. In: Roberton's Textbook of Neonatology, 2005, 4th Ed, London, Churchill Livingstone; 40.2: p. 521-45.
2. Hague KN. Definitions of bloodstream infection in the newborn. Pediatr Crit Care Med. 2005;6(6):S45-9.
3. Kermorvant-Duchemin E, Laborie S, Rabilland M, Lapillonne A, Claris O. Outcome and prognostic factors in neonates with septic shock. Pediatr Crit Care Med. 2008;9(2):186-91.
4. Fischer JE. Physician's ability to diagnose sepsis in newborns and critically ill children. Pediatr Crit Care Med. 2005;6(6):S120-5.
5. Shah GS, Budhathoki S, Das BK, Mandal RN. Risk factors in early neonatal sepsis. Kathmandu Univ Med J. 2006;4(2):187-91.
6. Isaacs D. Rationing antibiotic use in neonatal units. Arch Dis Child Fetal Neonatal Ed. 2000;82:F1-F2.
7. Hutzal CE, Boyle EM, Kenyon SC, Nash JV, Winsor S, Taylor DJ, et al. Use of antibiotics for the treatment of preterm partuition and prevention of neonatal morbidity: a metanalysis. Am J Obstet Gynecol. 2008;199(6):620e1-8.
8. Venkatesh MP, Garcia-Prats JA. Management of neonatal sepsis by gram negative pathogens. Expert Rev Anti Infect Ther. 2008;6(6):929-38.
9. Arnon S, Litmanovitz I. Diagnostic tests in neonatal sepsis. Curr Opin Infect Dis. 2008;21(3):223-7.
10. Isaacs D, Catherson J, Hope PL, Moxon ER, Wilkinson AR. Factors influencing colonisation with gentamicin resistant gram negative organisms in the neonatal unit. Arch Dis Child. 1988;63(5):533-5.
11. Lodha A, Furlan AD, Whyte H, Moore AM. Prophylactic antibiotics in the prevention of catheter-associated bloodstream bacterial infection in preterm neonates: a systematic review. J Perinatol. 2008;28(8):526-33.
12. Jardine LA, Inglis GD, Davies MW. Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters. Cochrane Database Syst Rev. 2008;23(1):CD006179.