Author/s:
Carr, JP;Burgner, DP;Hardikar, RS;Buttery, JP

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Empiric Antibiotic Regimens for Neonatal Sepsis in Australian and New Zealand Neonatal Intensive Care Units.

Original Article

Jeremy Carr[1], David Burgner[1,2,3,4], Rohan Hardikar[5], Jim Buttery[1,2,3,4,6]

1. Dept. of Infection and Immunity, Monash Children's, Melbourne Australia
2. Dept. of Paediatrics, Monash University, Australia
3. Murdoch Children's Research Institute, Melbourne Australia
4. Dept. of Paediatrics, University of Melbourne, Australia
5. Southern Clinical School, Monash University, Australia
6. The Ritchie Centre, Hudson Institute of Medical Research, Monash University, Australia

Corresponding Author

Jeremy Carr

Infectious Diseases Unit

Royal Children's Hospital Melbourne

Flemington Road, Parkville, 3052 Vic, Australia

Ph +61393455522

Jeremy.carr@rch.org.au

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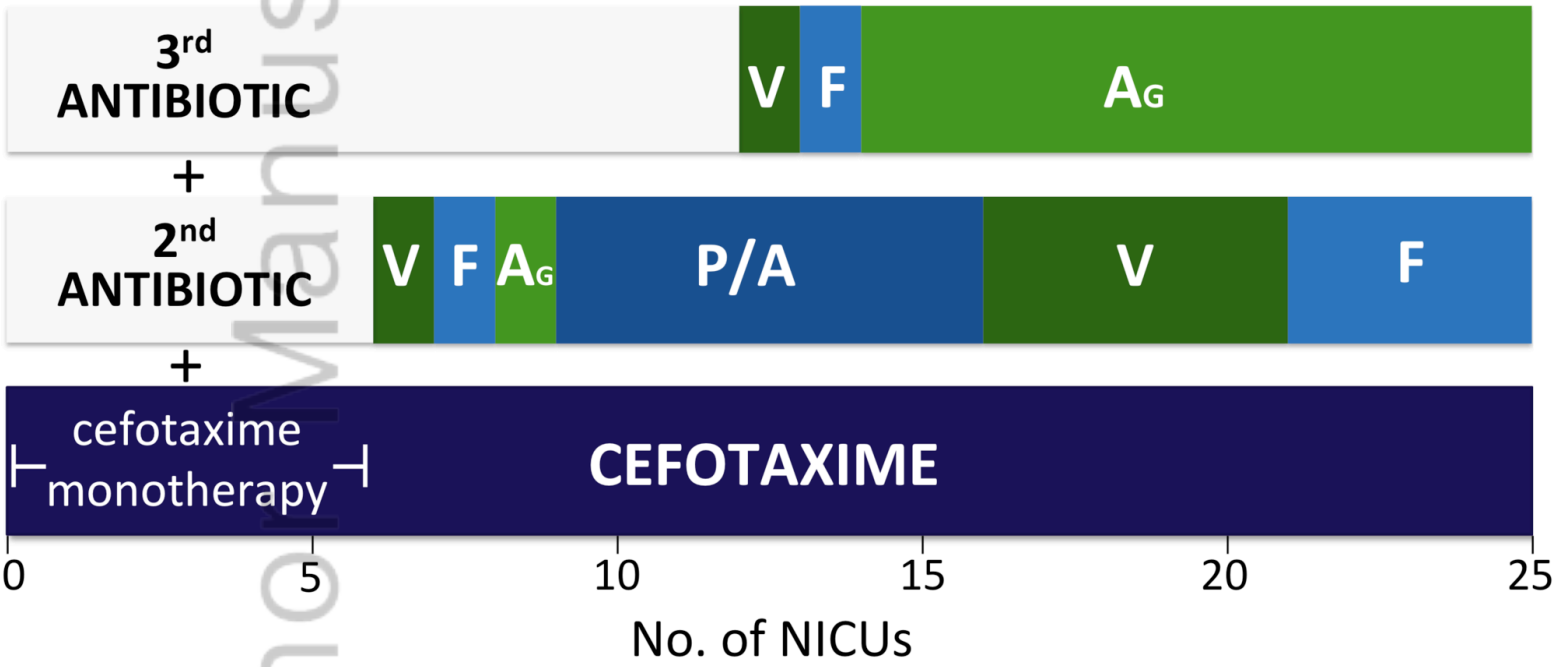

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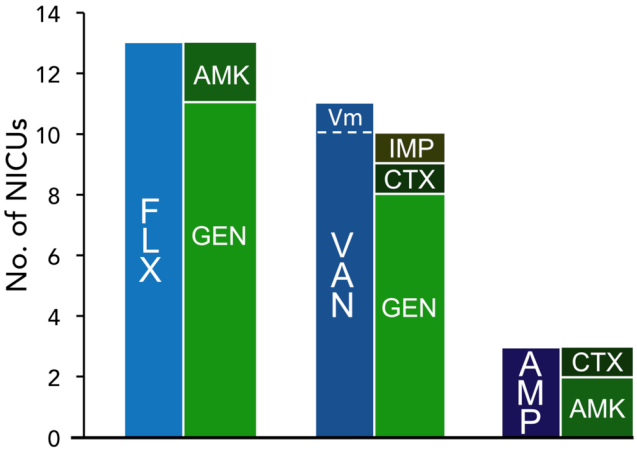

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Empiric Antibiotic Regimens for Neonatal Sepsis in Australian and New Zealand Neonatal Intensive Care Units

Abstract

Aim: Neonatal Sepsis remains an important cause of morbidity and mortality, and requires prompt empiric treatment. However only a minority of babies who receive antibiotics for suspected sepsis have an infection. Antimicrobial exposure in infancy has important short and long-term consequences. There is no consensus regarding empirical antimicrobial regimens.

Methods: Survey of empiric antimicrobial regimens in all tertiary neonatal intensive care units in Australia and New Zealand in 2013-14.

Results: All 27 units responded. For Early-onset Sepsis, all units used a combination of gentamicin with either penicillin or ampicillin. For Late-onset Sepsis, the frequency of units using empiric vancomycin (41%) versus empiric flucloxacillin (48%) was similar. Gestational age or the presence of a central venous catheter had little influence on using vancomycin instead of flucloxacillin. For Late-onset Sepsis with meningitis there was marked variation in antimicrobial combinations, with 15 different regimens described. 93% used a cefotaxime-based regimen, either as monotherapy (22%), or combined with a second (22%) or third (48%) agent. For suspected necrotising enterocolitis, 89% used an aminoglycoside, metronidazole and a penicillin. Historical outbreaks of multi-resistant organisms exerted long-term influence over regimen choice.

Conclusions: There was limited use of broad-spectrum agents such as carbapenems or third-generation cephalosporins. In this region with low MRSA prevalence, empiric vancomycin use was common, selected for activity against coagulase-negative staphylococci (CoNS). Empiric vancomycin is rarely necessary because CoNS are often contaminants and sepsis is rarely fulminant, occurring almost exclusively in extremely-low birth-weight infants. Implementation of appropriate, local antimicrobial policies is crucial to minimise antimicrobial exposure in this vulnerable population and halt the development of antimicrobial resistance.

What is already known on this topic

- Optimal empiric antimicrobial regimens for common neonatal infections are not well defined
- The majority of infants who commence antibiotics for suspected sepsis do not have an infection.
- Broad-spectrum antimicrobial use facilitates antibiotic resistance and additionally may have long-term health consequences through modulation of the early-life microbiome

What this paper adds

- Highlights the variation in antimicrobial regimens across all Australian and New Zealand tertiary Neonatal Intensive Care Units
- Demonstrates that the use of broad-spectrum antibiotics is limited, although the inclusion of empiric vancomycin is common but contentious.
- Reinforces the need for consistent antimicrobial policies to limit the development of antimicrobial resistance and safely minimise broad-spectrum antimicrobial exposure in the critical infant period.

Introduction

Sepsis remains an important cause of neonatal morbidity and mortality, and necessitates prompt recognition and treatment. Clinical signs are non-specific and laboratory investigations lack negative predictive value to confidently refute the presence of infection. Consequently, most infants who commence empiric antimicrobial therapy do not have an infection.[1, 2] Antimicrobial use promotes colonisation with resistant bacteria, predisposes to necrotising enterocolitis (NEC), invasive candidiasis, and may independently contribute to risk of death.[3-5] Exposure to antimicrobials in infancy may have broad and pervasive influence on life-long risk of both communicable and non-communicable disease through modulation of the early-life microbiome. [6, 7] Appropriate empiric antimicrobial regimens combined with antimicrobial stewardship programs (ASP) may minimise adverse consequences. Implementation is challenging in light of lack of consensus on clinical sepsis definitions, the differing empiric regimens used and paucity of evidence for commonly included broad-spectrum antibiotics such as vancomycin or 3rd generation cephalosporins.[8-15]

The Australian and New Zealand Neonatal Network (ANZNN) is a collaborative body of all neonatal intensive care units in Australia and New Zealand that monitors outcomes from high-risk neonates. Crude rates of infection are included, but not include organism and susceptibility data or antimicrobial use. We surveyed all tertiary Neonatal Intensive Care Units (NICUs) of the ANZNN to characterise empiric antimicrobial regimens for common neonatal infections.

Methods

An on-line REDCAP-based[16] survey of unit-wide antimicrobial policies was distributed to all tertiary NICUs in Australian and New Zealand in 2013-14. Permission to conduct the survey was obtained from the ANZNN, and a consultant neonatologist completed the survey at each site (head of unit or designated consultant responsible for infection). The questionnaire surveyed empiric antibiotic regimens for EOS, LOS, and NEC, assuming that microbiology results for each scenario were not yet available (online supplement). LOS regimens were stratified as

'meningitis' or 'not meningitis' based on abnormal cerebrospinal fluid (CSF) microscopy and biochemistry, although abnormal CSF parameters were intentionally not defined, given lack of consensus. The survey included modifications to empiric regimens, based on factors such as birth weight, gestational age or the presence of a central line. Diagnostic methods, treatment duration, local epidemiology and antimicrobial resistance patterns were outside the scope of this questionnaire.

Results

All 27 tertiary NICUs in Australia (21) and New Zealand (6) completed the survey. The cut-off between EOS and LOS was defined as clinical infection developing ≥ 48 hours after birth in 63% of units, as ≥ 72 hours in 26% and ≥ 7 days of life in 11%.

Early-onset sepsis (EOS): All units used gentamicin in combination with either benzylpenicillin (67%) or ampicillin (30%), with one unit allowing consultant discretion between choosing ampicillin or penicillin. No unit used cephalosporins or carbapenems in their first-line empiric EOS regimen.

Late-onset sepsis (LOS) without meningitis: There were eight different empiric antibiotic regimens across the 27 NICUs (Figure 1). The frequency of empiric use of flucloxacillin (48%) was similar to vancomycin (41%). Gram-negative coverage was most often an aminoglycoside (85%, either gentamicin (70%), or amikacin (15%)) followed by cefotaxime (7%) or imipenem (4%). One unit specified the use of vancomycin monotherapy if central line infection was suspected, and added either cefotaxime or gentamicin if the baby was clinically 'unwell', or alternatively commenced piperacillin-tazobactam.

LOS with presumed meningitis: There were 15 different regimens amongst the 27 units. The complexity of regimen choice is depicted schematically in Figure 2. Ninety-three per cent of NICUs used cefotaxime-containing regimens. Of these, six (22%) used cefotaxime monotherapy, while 19 (70%) combined cefotaxime with a second (22%) and third (48%) antimicrobial. The difference between regimens chosen for LOS with and without meningitis for each unit varied. Nine NICUs added cefotaxime

to their standard LOS regimens, three substituted an aminoglycoside for cefotaxime, and four units modified empiric LOS regimens to include either ampicillin or penicillin. Two units used non-cefotaxime based regimens: one unit used ceftazidime due to a period of higher incidence of pseudomonas sepsis three years before the survey; the other unit used imipenem and vancomycin for LOS with or without meningitis. This regimen was initiated in the context of a resolved outbreak of ESBL producing *Klebsiella pneumoniae* eighteen years prior to the survey but had remained the current first-line recommendation.

Modifications to empiric LOS regimens: Of the 13 NICUs who used empiric flucloxacillin for LOS, only three would switch to vancomycin in the presence of a central venous catheter. For LOS, one unit used flucloxacillin for infants with corrected age above 29 weeks, and vancomycin in infants under 29 weeks corrected age. No NICU modified empiric antibiotics according to birth weight.

Necrotising enterocolitis (NEC): Eight-nine per cent of units prescribed an aminoglycoside and metronidazole, combined with ampicillin (44%), penicillin (11%), flucloxacillin (15%) or vancomycin (19%). Two units (7%) used piperacillin-tazobactam monotherapy and one unit used gentamicin combined with amoxycillin-clavulanate. No unit used clindamycin.

Discussion

This survey of all NICUs in Australian and New Zealand highlights variance in empiric antimicrobial regimens for common neonatal infections. This is most pronounced for LOS with meningitis, with fifteen different antibiotic regimens across 27 units. In the absence of robust evidence from randomised controlled trials, previous surveys have also highlighted the variation in antimicrobial use, particularly the inclusion of vancomycin or broad-spectrum cephalosporins.[8, 10, 14, 15, 17]

The temporal cut-off between EOS and LOS (to denote vertical versus nosocomial infection) is indistinct and published definitions vary between 48, 72 hours or 7

days.[12, 18-20] Our regional survey reflected this lack of consensus, despite the ANZNN distinguishing between EOS and LOS at 48 hours.[21]

All EOS regimens provided adequate coverage for the major pathogens, including Listeria, and no NICU used vancomycin or a cephalosporin. The causative organisms of LOS in Australia and New Zealand tertiary NICUs are similar to those described from other developed settings, although antimicrobial susceptibilities vary.[1, 22] Coagulase-negative staphylococci (CoNS) account for approximately half of all culture-positive episodes.[1, 22] For LOS, most units used an aminoglycoside in combination with either flucloxacillin or vancomycin in equal proportion. Two units (7%) did not use an empiric regimen with activity against methicillin-sensitive *Staphylococcus aureus* (MSSA), while one other unit relied upon cefotaxime to cover MSSA. A 2003 survey of several Australian NICUs also showed an equal proportion of units using either vancomycin or flucloxacillin, whilst in a recent European survey only 15% of units included vancomycin in empiric LOS regimens.[17, 23] Our survey was conducted in region with a low prevalence of methicillin-resistant *Staphylococcus aureus*,[24] thus the rationale for empiric vancomycin is primarily for CoNS, as over 90% of isolates are resistant to flucloxacillin.[22, 25] Although CoNS accounts for over 50% of LOS isolates in some series, their true contribution to sepsis is not clearly defined because differentiation between CoNS as a contaminant or a pathogen is problematic and definitions vary between studies.[1, 22, 26] The rate of neonatal *Staphylococcal* infection is also significantly influenced by infection control and prevention practices.[27] CoNS are low virulence organisms typically causing indolent disease, with fulminant sepsis occurring in less than 1% of cases[28] and deaths attributed to CoNS are almost exclusively in extremely low birth weight infants.[26] CoNS-related mortality is difficult to estimate but is lower than previous studies suggested, with combined direct and indirect attributable mortality ranging from 0.33% - 5%.[23, 26, 28, 29]

No studies have demonstrated a benefit of empiric vancomycin for CoNS sepsis, although existing studies are mostly retrospective and underpowered to detect a low attributable mortality of CoNS sepsis.[23, 30-34] Adverse effects associated with

vancomycin include nephrotoxicity, the selection of vancomycin-resistance in CoNS and Enterococci (VRE), resistant Gram-negative colonisation and, *Staphylococcus aureus* colonisation and infection.[35-39] Neonatal vancomycin dosing is problematic and there is often delay in obtaining therapeutic levels, which is thought to correlate with both treatment failure and the development of resistance. In considering the uncertain benefit of vancomycin with potential adverse consequences, a successful and safe strategy to limit vancomycin use in most cases is delaying the initiation of vancomycin until identification of a clinically-significant CoNS in blood culture.[31]

Aminoglycosides are the mainstay for empiric Gram-negative coverage in Australia and New Zealand. Only seven per cent of NICUs used an empiric 3rd generation cephalosporin for LOS without meningitis. The use of a cephalosporin confers no benefit in antimicrobial spectrum over a beta-lactam/aminoglycoside combination.[40] Several studies have demonstrated an association between cephalosporin use and increased rates of antimicrobial resistance within units, and some indicate increased morbidity or mortality.[5, 41]

Variation between units was particularly evident when meningitis was suspected, and the complexity of antimicrobial combinations, depicted in Figure 2, cannot be explained by antimicrobial spectrum or likely susceptibility patterns. One in five units did not cover Listeria infection. The use of dual Gram-negative agents, particularly the combination of an aminoglycoside and a third-generation cephalosporin was common. There is no literature supporting the use of dual Gram-negative antimicrobials in meningitis. The use of 'synergistic' gentamicin in meningitis caused by Gram-positive organisms is based solely on *in vitro* models and animal studies, with no difference in clinical outcomes in infants.

Antibiotic regimens for presumed NEC differed predominantly in choice of Gram-positive cover. The inclusion of flucloxacillin by some units relates to the low discrimination between the signs of early NEC and septic ileus, where *Staphylococcus aureus* is a potential (and fulminant) pathogen.[24, 42] The use of vancomycin may reflect the known association between CoNS and NEC. Similar to CoNS sepsis, NEC

associated with CoNS bacteraemia has a low mortality.[43] The long-term effects of the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam on the development of resistance are not well studied. A recent Cochrane review concluded there was insufficient evidence to recommend a specific antibiotic regimen for NEC.[44]

The strengths of this study include that this is the first regional survey of neonatal antibiotic practice in tertiary NICUs and had a complete response rate. We acknowledge some inevitable shortcomings, including that surveying a single neonatologist for each unit may not adequately capture within-unit differences in practice, despite the survey stipulating unit-wide policies or practice. Our survey does not assess actual antibiotic use[45], adherence to empiric protocol, or local antimicrobial stewardship resources, which are important factors in reducing antibiotic exposure. Neonatal units constitute a significant proportion of paediatric inpatient antimicrobial use and the majority of antibiotic use for suspected sepsis will follow institutional protocol. Thus defining the optimal empiric regimen is an integral component of neonatal antimicrobial stewardship. Further research should clarify the role of vancomycin in LOS, including the efficacy of delayed or stratified use, although an adequately powered study would require a large study population. The persistent use of ceftazidime and imipenem following outbreaks of resistant organisms many years earlier revealed in this survey highlights the need for timely and regular review of outbreak control strategies to return to a more narrow-spectrum regimen as soon as safely possible.

The use of broad-spectrum antibiotics in empiric regimens in Australia and New Zealand is relatively limited, with the exception of vancomycin, which has a limited empiric role in settings with low MRSA prevalence. Currently, there is a low prevalence of multi-resistant organisms in Australian and New Zealand neonatal units. In Asia, there is widespread resistance in Gram-negative organisms to first line antibiotics, ampicillin and gentamicin, as well as cephalosporins.[46, 47] Similar patterns of resistance are seen in many other regions.[48] There is a time-critical opportunity to preserve the low rate of antimicrobial resistance in Australia and New

Zealand. Development and broad implementation of evidence-based empiric antimicrobial regimens informing both choice and duration of therapies, together with recent successes in antimicrobial stewardship programs and the reduction in line related blood-stream infections using multi-component " bundled" interventions, should better protect our most vulnerable newborns.

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Figure Titles & Legends

Figure 1. Empiric Late-onset Sepsis regimens (non-meningitis) grouped by primary Gram-positive antibiotic.

Legend: **FLX** flucloxacillin; **VAN** vancomycin; **AMP** ampicillin; **GEN** gentamicin; **AMK** amikacin; **CTX** cefotaxime; **IMP** imipenem; **Vm** vancomycin monotherapy ± gentamicin or cefotaxime.

Figure 2. Late-onset Sepsis with suspected meningitis*:* Schematic depiction of variance in cefotaxime-based empiric regimens

Legend: **V** vancomycin; **F** flucloxacillin; **AG** aminoglycoside; **P/A** penicillin *or* ampicillin