Antibiotic prescribing in neonatal sepsis: an Australian nationwide survey

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ABSTRACT

Objective To evaluate quality and variation in antibiotic prescribing for neonatal sepsis.

Design We analysed prescribing in hospitalised neonates using the National Antimicrobial Prescribing Survey in Australian neonates from 1 January 2014 to 31 December 2018.

Setting Data from antibiotic point prevalence surveys performed in hospitals, ranging from rural hospitals to tertiary paediatric and maternity hospitals within Australia.

Patients Admitted neonates <28 days of age from participating hospitals.

Main outcome measures Variation and appropriateness in prescribing for neonatal sepsis and variation in dosing for gentamicin and benzylpenicillin across hospitals.

Results A total of 415 prescriptions among 214 neonates from 39 different hospitals were included. The majority of prescriptions (342, 82.4%) were for neonates <7 days of age. The most commonly prescribed antibiotics were gentamicin and benzylpenicillin, with 323 (77.8%) prescriptions. Dosing variability was substantial, with doses ranging from 2 to 8 mg/kg for gentamicin (median 5 mg/kg, IQR 4–5) and from 45 to 72 mg/kg for benzylpenicillin (median 60 mg/kg, IQR 50–60), although only 13 (3.2%) and 19 (4.6%) prescriptions were locally assessed as inappropriate or non-compliant with guidelines, respectively. At time of audit, 22% of antibiotics had been given for more than 48 hours and 9% more than 72 hours, although microbiologically confirmed infection was documented in only nine (4.2%) neonates.

Conclusions Prescribing for neonatal sepsis was dominated by use of benzylpenicillin and gentamicin with substantial variation in dosing. A small minority had culture-confirmed infection. Efforts to standardise antibiotic dosing and duration for suspected neonatal sepsis are recommended.

INTRODUCTION

The neonatal period is the most vulnerable time of life, with neonatal mortality accounting for almost 50% of deaths in children under 5 years and approximately 2.5 million deaths globally in the first month of life in 2018.1 In Australia, despite a comparatively low neonatal mortality rate, 2 per 1000 live births compared with 18 per 1000 globally,2 perinatal infection is identified as the primary cause of neonatal death in 10.6% of Australian neonatal deaths.2 Risk factors for neonatal sepsis mortality include prematurity, lower postnatal age and immunological immaturity.3,4 Neonates who require hospitalisation may have additional risk factors for sepsis, including central venous catheters and mechanical ventilation. Clinical signs of neonatal sepsis are often non-specific5; thus, empiric antibiotic therapy is commonly prescribed for hospitalised neonates.6 The majority of neonates treated empirically for sepsis, however, do not have confirmed infection on final assessment.7,8

Unintended adverse consequences of widespread antibiotic use for neonates have been increasingly recognised, with calls for better understanding of sepsis epidemiology and efforts to promote judicious prescribing.9 The Kaiser Permanente Early Onset Sepsis Calculator is one tool used to predict risk of microbiologically confirmed infection and reduce unnecessary investigations and...
antibiotic therapy with some success. This only applies to neonates with early-onset sepsis (EOS), however, and similar tools for late-onset sepsis (LOS) are lacking.

In recognition that the epidemiology of sepsis in neonates varies with age, it is commonly divided into EOS and LOS. While the risk and microbiology of sepsis in the first few days of life are reported to be substantially influenced by antenatal and intrapartum factors, sepsis beyond the first few days is likely influenced to a greater extent by the postnatal environment, although the utility of this division across global settings has been challenged. The definition of EOS versus LOS also varies between studies. The Australian and New Zealand Neonatal Network defines EOS as neonatal sepsis with initial symptoms beginning <48 hours of life (2 days). Common pathogens identified in EOS have been better characterised than those causing LOS in Australia, although both have been described in the UK.

In this study we aimed to report on antimicrobial prescribing for neonatal sepsis of all types, using a national data set from Australia. Antibiotic use and appropriateness for indications other than sepsis, such as prophylaxis, are not included in this analysis.

**METHODS**

We obtained de-identified data from the National Antimicrobial Prescribing Survey (NAPS) database of point prevalence prescribing surveys for Australian hospitals from all six Australian states and two territories (from 1 January 2014 to 31 December 2018). Participation in these surveys is voluntary and data are submitted through a web-based interface to a central database. Hospitals can participate in these surveys whenever they choose, although most participate annually. Survey methodology has been described previously; in brief, the data set includes antimicrobial usage (agent, dose, frequency, route); baseline demographics (age, gender, hospital location, funding type (public/private), hospital size); infection site and type; adherence with local or national Australian antibiotic guidelines; and antimicrobial appropriateness. Local guidelines include any locally endorsed Australian antibiotic guidelines; and antimicrobial appropriateness. Local guidelines include any locally endorsed hospital, network or regional guidelines, other than the priateness. Local guidelines include any locally endorsed Australian antibiotic guidelines; and antimicrobial appropriateness. Local guidelines include any locally endorsed Australian antibiotic guidelines; and antimicrobial appropriateness. Local guidelines include any locally endorsed Australian antibiotic guidelines; and antimicrobial appropriateness. Local guidelines include any locally endorsed Australian antibiotic guidelines; and antimicrobial appropriateness.

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**RESULTS**

**Demographics**

Among 884 neonatal prescriptions between 1 January 2014 and 31 December 2018, 415 (46.9%) prescriptions were recorded as given for sepsis. These prescriptions were for 214 neonates from 39 hospitals. All Australian states and territories were represented apart from the Northern Territory. Hospitals included specialist women’s hospitals or paediatric hospitals with tertiary neonatal intensive care units, as well as general public and private hospitals. A large majority of included hospitals (88.7%) were in metropolitan areas. Female neonates accounted for 184 (44.3%) prescriptions and the rest were for male neonates. The number of prescriptions varied by year (table 1). The majority of prescriptions were for neonates <7 days of age (342, 82.4%). Where this could be assessed, 71% (245 of 345) of prescriptions were for EOS and 29% (100 of 345) for LOS. Premature neonates accounted for 123 prescriptions (54.4% of prescriptions for which gestational age was available). The median birth weight was 2.9 kg (IQR 1.9–3.4). Demographic details are shown in full in table 1.

**Antibiotic type and duration**

The Drug Utilization 90%, which refers to the number of antibiotics accounting for 90% of usage when ranked by frequency, included a total of five antibiotics. In descending order these were gentamicin, benzylpenicillin, cefotaxime, ampicillin and fluoroquinolones. Twenty (9.3%) neonates were prescribed one antimicrobial for sepsis, 187 (87.4%) neonates two antimicrobials and 7 (3.3%) neonates three antimicrobials. There were 323 (77.8%) prescriptions of either gentamicin...
Table 1 Demographic details

| Demographics                  | Total prescriptions (415) | %  |
|-------------------------------|--------------------------|----|
| Gestational age (weeks)       |                          |    |
| <25                           | 20                       | 4.8|
| 25 to <30                     | 32                       | 7.7|
| 30 to <35                     | 52                       | 12.5|
| 35 to <37                     | 21                       | 5.1|
| ≥37                           | 101                      | 24.3|
| Not stated                    | 189                      | 45.5|
| Postnatal age (days)          |                          |    |
| <7                            | 342                      | 82.4|
| 7 to <15                      | 38                       | 9.2|
| 15 to <28                     | 35                       | 8.4|
| Sex: female                   | 184                      | 44.3|
| Median (IQR) weight (kg)      | 2.9 (1.9–3.4)            | NA |
| Records by year of survey     |                          |    |
| 2014                          | 56                       | 13.5|
| 2015                          | 118                      | 28.4|
| 2016                          | 63                       | 15.2|
| 2017                          | 87                       | 21.0|
| 2018                          | 91                       | 21.9|
| In NICU/ICU*                  | 174                      | 41.8|
| Hospital type                 |                          |    |
| Specialist women’s            | 161                      | 38.8|
| Specialist children’s         | 76                       | 18.3|
| Specialist women’s and children’s | 31                   | 7.5|
| Other public hospitals        | 134                      | 32.2|
| Private hospitals             | 6                        | 1.5|
| Unpeered/unknown              | 7                        | 1.7|
| Hospital location             |                          |    |
| Major city                    | 368                      | 88.7|
| Inner regional                | 28                       | 6.7|
| Outer regional                | 19                       | 4.6|

*NICU/ICU status not stated for 77 prescriptions.
ICU, intensive care unit; NA, not applicable; NICU, neonatal intensive care units.

or benzylpenicillin, and 133 of 214 (62.1%) neonates were prescribed both benzylpenicillin and gentamicin. Antibiotics most frequently prescribed in total and for EOS/LOS are shown in tables 2 and 3. At audit, 48% of antibiotics had been given for >24 hours, 22% for >48 hours and 9% for >72 hours (figure 1). Microbiologically confirmed infection was documented in only 15 (3.6%) prescriptions among 9 (4.2%) neonates (table 4). Antibiotic duration was significantly longer in specialist hospitals (median 2 days, IQR 1–3 days) compared with non-specialist hospitals (median 1 day, IQR 1–1.5 days; p<0.0001) (online supplementary appendix figure 2) but did not differ by metropolitan versus rural hospital prescriptions.

Appropriateness and guideline compliance
Overall 400 of 415 (96.4%) prescriptions were assessed by local hospital auditors as appropriate and 13 (3.1%) inappropriate, with 230 (79.5%) prescriptions assessed as compliant with local guidelines and 53 (12.8%) prescriptions as compliant with the national Therapeutic Guidelines. Nineteen (4.6%) prescriptions were assessed as non-compliant with guidelines. Detailed appropriateness and compliance assessment is displayed in online supplementary appendix table 1. Appropriateness was reported as similar for specialist and non-specialist hospitals (98% vs 95% appropriate), but reported guideline compliance was significantly higher in specialist hospitals (97.3% compared with 91.8%, respectively; p=0.013). Metropolitan hospitals had higher reported appropriateness compared with rural hospitals (98.1% vs 87.2%; p=0.0001) and guideline compliance (96.9% vs 83%; p=0.0001).

Dosing variability: gentamicin and benzylpenicillin
Gentamicin dosing and frequency information was available for 178 prescriptions. The dose varied from 2 to 8 mg/kg (median 5 mg/kg, IQR 4–5). Gentamicin dose variability is shown in figure 2A. Benzylpenicillin dosing and frequency information was available for 143 prescriptions. The dose varied from 45 to 72 mg/kg (median 60 mg/kg, IQR 50–60). Benzylpenicillin dose variability is shown in figure 2B. Dosing frequency also varied, although the majority of neonates received 24-hourly gentamicin and 12-hourly benzylpenicillin (online supplementary appendix table 2). Dosing for benzylpenicillin did not differ by hospital location (metropolitan vs rural) or by specialist/non-specialist hospital. Gentamicin dosing was significantly lower (p<0.0001) in non-specialist hospitals (median 4.4 mg/kg/dose, IQR 3.9–5 mg/kg/dose) compared with specialist hospitals (median 5 mg/kg/dose, IQR 4.6–5.1 mg/kg/dose). Gentamicin dosing was also significantly lower (p<0.0001) in rural hospitals (median 3.9 mg/kg/dose, IQR 2.5–4.5 mg/kg/dose) compared with metropolitan hospitals (median 5 mg/kg/dose, IQR 4.5–5 mg/kg/dose).

DISCUSSION
In this study, the largest nationwide analysis of prescribing for neonatal sepsis in Australia, we found a strong preference for use of gentamicin and benzylpenicillin for treatment of neonatal sepsis/risk of sepsis but substantial variation in dosing of these agents. The study included a broad range of gestational ages and a variety of hospital types across Australia, but most neonates treated for sepsis were <7 days of age. Only 4% of neonates had microbiologically confirmed infection. Locally assessed...
Table 2  Antibiotics by frequency prescribed

| Antibiotics             | Prescriptions* | Percentage | Cumulative percentage |
|-------------------------|----------------|------------|-----------------------|
| Gentamicin              | 179            | 43.1       | 43.1                  |
| Benzylpenicillin (penicillin G) | 144          | 34.7       | 77.8                  |
| Cefotaxime              | 26             | 6.3        | 84.1                  |
| Ampicillin              | 18             | 4.3        | 88.4                  |
| Flucloxacillin          | 13             | 3.1        | 91.6                  |
| Vancomycin              | 13             | 3.1        | 94.7                  |
| Amoxicillin (amoxycillin)| 9             | 2.2        | 96.9                  |
| Meropenem               | 6              | 1.45       | 98.3                  |
| Benzathine penicillin   | 4              | 0.96       | 99.3                  |
| Amphotericin B liposomal| 1              | 0.24       | 99.5                  |
| Azithromycin            | 1              | 0.24       | 99.8                  |
| Ceftriaxone             | 1              | 0.24       | 100                   |

*Total=415 prescriptions in 214 neonates.

Table 3  Top 5 antibiotics by frequency prescribed and sepsis type

| Antibiotic: all        | Prescriptions | Cumulative percentage |
|------------------------|---------------|-----------------------|
|                        | Total=415, n (%) |                |
| Gentamicin             | 179 (43.1)    | 43.1                  |
| Benzylpenicillin (penicillin G) | 144          | 34.7                  |
| Cefotaxime             | 26 (6.3)      | 84.1                  |
| Ampicillin             | 18 (4.3)      | 88.4                  |
| Flucloxacillin         | 13 (3.1)      | 91.6                  |

| Antibiotic: EOS        | Prescriptions | Cumulative percentage |
|------------------------|---------------|-----------------------|
|                        | Total=245, n (%) |                |
| Gentamicin             | 119 (48.6)    | 48.6                  |
| Benzylpenicillin (penicillin G) | 100         | 89.4                  |
| Ampicillin             | 12 (4.9)      | 94.3                  |
| Amoxicillin            | 5 (2)         | 96.3                  |
| Benzathine penicillin  | 3 (1.2)       | 97.6                  |

| Antibiotic: LOS        | Prescriptions | Cumulative percentage |
|------------------------|---------------|-----------------------|
|                        | Total=100, n (%) |                |
| Gentamicin             | 31 (31)       | 31                    |
| Cefotaxime             | 18 (18)       | 49                    |
| Benzylpenicillin (penicillin G) | 16         | 65                    |
| Vancomycin             | 11 (11)       | 76                    |
| Flucloxacillin         | 10 (10)       | 86                    |

EOS, early-onset sepsis; LOS, late-onset sepsis.

appropriateness and guideline compliance were high but varied by hospital type and location.

Large-scale analysis of antibiotic prescribing and appropriateness for neonatal sepsis has not been reported in Australia. Information on neonatal empiric guideline use and prescribing has been reported from selected large neonatal intensive care units, but this excludes many health services providing neonatal care. Hospitals use a variety of different guidelines for selection and dosing of empiric antibiotic therapy in neonates. Benzylpenicillin and gentamicin are recommended for empiric treatment of neonatal sepsis in current national guidelines and are appropriate empiric therapy for the majority of organisms responsible for EOS in Australia. This study confirms these are frequently used currently, although with considerable variation in administration.

In our study, only a small number of sepsis prescriptions (4%) were for microbiologically confirmed infections. While antibiotics may be life-saving, they are also associated with adverse effects, including impact on the neonate microbiome, with potential long-term atopic and metabolic consequences of antibiotics in early life including asthma and obesity. A rational prescribing approach includes ‘making a (differential) diagnosis, estimating prognosis, establishing the goals of therapy, selecting the most appropriate treatment and monitoring the effects...
of that treatment’.28 In contrast, prescribing for risk of sepsis in neonates generally requires commencement of antibiotic therapy, despite the fact that most will not have culture-confirmed infection. Current challenges in refining and standardising therapy include a lack of data-driven consensus definition for neonatal sepsis and lack of sufficiently rapid, sensitive and specific diagnostic tests during the early phase of illness to rule in/out serious infection.29 More sensitive and specific rapid diagnostic tools requiring minimal sample volumes are required to further improve care and outcomes for suspected neonatal sepsis.

Dosing variation in the small number of drugs commonly used to treat neonatal sepsis represents an opportunity to standardise and potentially improve care. A survey of six Australian tertiary neonatal units conducted in 2012 demonstrated substantial variation in dosing for vancomycin and gentamicin in neonates, with gentamicin, benzylpenicillin and vancomycin the most commonly prescribed drugs for systemic therapy.22 A survey of neonatal intensive care units from 21 European countries, with 586 systemic antibiotic prescriptions for infants up to 90 days of age, reported a tendency of overdosing penicillins and underdosing vancomycin and gentamicin, relative to guidelines.30 Although we found variation both above and below recommended doses for benzylpenicillin and gentamicin in neonates treated for sepsis, we also found a tendency of underdosing gentamicin in non-specialist and non-metropolitan hospitals, a cause for concern. One potential source of dosing variation is use of birth weight rather than measured weight in neonates and rounding of doses for drug dose calculations. In one study of more than 9000 neonates over a 20-year period, weight error due to digit bias (whereby round numbers are favoured) improved over 20 years but was still evident in neonates between 1000 and 4500 g at ≤5%.31 Relative to body size, this phenomenon accounts for additional variation not seen in the adult population, where standardised doses are used, and the implications of this variation for research and practice improvement remain insufficiently understood.

Although local and international guidelines available for management of neonatal sepsis are available,32 national guidelines for neonatal sepsis prescribing did not exist during the period of this study. These are now available, however, with national Therapeutic Guidelines updated in mid-2019 to include recommendations for treatment of neonatal sepsis and selected other neonatal infections. These subscription guidelines are widely available in Australian hospitals and contain evidence-based dosing recommendations, selected by expert consensus group review and dosing aligned with recommendations from the Australasian Neonatal Medicines Formula (ANMF) group. The ANMF group provides freely

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**Table 4** Neonates with microbiologically confirmed infection

| Microbiologically confirmed infection type | Prescriptions (%) | Neonates (%) |
|------------------------------------------|-------------------|--------------|
| Coagulase-negative staphylococcal bacteraemia | 7 (1.7) | 5 (2.3) |
| Candidaemia* | 4 (1.0) | 2 (0.9) |
| Other† | 4 (1.0) | 2 (0.9) |
| Total‡ | 15 (3.6) | 9 (4.2) |

*One infant had *Candida glabrata* and coagulase-negative *Staphylococcus* in blood cultures and was treated with liposomal amphotericin B. The other had *C. albicans* in blood culture. This infant was treated with fluconazole for indication ‘candidaemia’ and benzylpenicillin and cefotaxime for indication ‘sepsis’.
†One infant had Gram-positive cocci detected in blood culture, awaiting species confirmation at time of audit. The other had pneumonia with *Klebsiella oxytoca* isolated from endotracheal tube aspirate culture.
‡Only one infant with microbiologically confirmed infection met the criteria for early-onset sepsis, with as yet unidentified Gram-positive cocci in blood culture.

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**Figure 2** Individual dose ranges for gentamicin and benzylpenicillin (whole mg/kg). (A) Gentamicin (n=178): median dose 5mg/kg (IQR 4–5mg/kg). Dots represent outliers; one 52 mg/kg dose omitted from the figure, as apparent 10-fold error. (B) Benzylpenicillin (n=143): median dose 60 mg/kg (IQR 50–60); one 6 mg/kg dose omitted from the figure, as apparent 10-fold error.
available, evidence-based and regularly updated medic- 
cine guidelines for neonates. Both the ANMF and 
Therapeutic Guidelines recommend dosing of 5 mg/ 
kg for gentamicin and 60 mg/kg for benzylpenicillin 
(90 mg/kg for meningitis), with frequency dependent on 
gestational and postnatal age. These may serve as refer-
ces for future assessment of neonatal sepsis prescribing 
as national standard recommendations.

Over 20% of antibiotics had been prescribed for 
>48 hours at time of audit, although only 4% of neonates 
had microbiologically confirmed infection documented. 
Given that the majority of potential pathogens in neonatal 
sepsis are identified within 36–48 hours, this may repre-
sent excessive antibiotic therapy and provides an oppor-
tunity for quality improvement. Hospital antimicrobial 
stewardship teams may not include neonatal pharma-
cologists or neonatal infection specialists, and thus the 
recently nationally available guidelines for sepsis and 
antimicrobial use in neonates, listed above, may provide a 
more robust framework for assessment and promotion of 
the most appropriate therapy. Since most prescribing for 
neonatal sepsis in Australia includes only a small number 
of drugs, as we have shown, efforts to improve consistency 
in antimicrobial use is a substantial limitation, although it 
reinforces our point that diversity of guidelines is a major challenge to 
achieving standardised prescribing. In addition to this, 
as we have described above, it is possible that compliance 
and appropriateness have been overattributed by local 
assessors, although these may in future be ameliorated 
by new national guidelines and further assessor training. 
We also do not currently have information on the propor-
tion of neonates in each hospital who were not prescribed 
antibiotics. Weight was not a mandatory field in the NAPS 
tool at the time of survey and we did not include neonates 
who did not have a weight recorded, as we required this to 
calculate doses by weight for this study. For future surveys, 
mandatory inclusion of weight could improve the tool’s 
utility for antimicrobial prescribing to neonates and chil-
dren. Gestational age was not stated in 45.5% of cases, and 
this also limits our ability to interpret prescribing patterns 
and appropriateness with reference to this. We also made 
assumptions based on age to calculate EOS and LOS as 
this was not directly entered by local assessors, and these 
results must be interpreted with caution. The data here 
may not be applicable to countries with high rates of drug-
resistant organisms causing neonatal sepsis as these are 
likely to have different prescribing choices. In this 
study, we did not have access to local antibiograms, but the 
proportions of gentamicin and penicillin used here are in 
keeping with available national data showing relatively low 
rates of drug-resistant pathogens in neonatal sepsis.

CONCLUSIONS

In this nationwide survey we have identified substantial 
variability in dosing of benzylpenicillin and gentamicin, 
the two most commonly prescribed antibiotics for 
neonatal sepsis in this study. Only a small minority of 
neonates treated for sepsis have culture-confirmed infec-
tion. Efforts to optimise therapy for treatment of neonatal 
sepsis and reach consensus for therapy, including 
understanding prescribing practices and implementing 
national guidelines, are recommended.

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