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Antibiotic prescribing in neonatal sepsis: a nationwide survey

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Abstract

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

Design: We analysed prescribing in hospitalized neonates, using the National Antimicrobial Prescribing Survey (NAPS) 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 maternal 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 2mg/kg to 8mg/kg for gentamicin (median 5mg/kg, IQR 4-5mg/kg) and 45-72mg/kg for benzylpenicillin (median 60mg/kg, IQR 48-64). Thirteen (3.2%) and 19 (4.6%) of prescriptions were deemed inappropriate or non-compliant with local or national guidelines, respectively. At time of audit, 47.5% of antibiotics had been given for 2 or more completed days and microbiologically confirmed infection was documented in only 9 neonates (4.2%).

Conclusions: Prescribing for neonatal sepsis was dominated by use of benzylpenicillin and gentamicin with substantial variation in dosing. Many prescriptions were given for at least 48 hours despite few confirmed infections. 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 those aged <28 days in 2017.[1] In Australia, despite a comparatively low neonatal mortality rate: 2.3 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.[3] Risk factors for neonatal sepsis mortality include prematurity, lower postnatal age and immunologic immaturity.[4,5] 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-specific,[6] thus empiric antibiotic therapy is commonly prescribed for hospitalized neonates.[7] The majority of neonates treated empirically for sepsis, however, do not have confirmed infection on final assessment.[8,9]

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.[10] 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.[11] This only applies to neonates with early-onset sepsis, however, and similar tools for late-onset sepsis are lacking.

In recognition that epidemiology of sepsis in neonates varies with age, it is commonly divided into early-onset sepsis (EOS) and late-onset sepsis (LOS). While risk and microbiology of sepsis in the first few days of life is 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 post-natal environment, though the utility of this division across global

settings has been challenged.[12] 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).[13] Common pathogens identified in early-onset neonatal sepsis have been better characterised than those causing late-onset sepsis in Australia, though both have been described in the United Kingdom.[7,14]

In this study we aimed to report on antimicrobial prescribing for neonatal sepsis of all types in neonates, using a national dataset 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 NAPS database of point-prevalence prescribing surveys for Australian hospitals from all 6 Australian states and 2 territories (1 January 2014 to 31 December 2018).[15] Participation in these surveys is voluntary and data are submitted through a web-based interface to a central database.[15] Survey methodology has been described previously.[16,17] Appropriateness assessments were conducted by trained local surveyors as described previously[18,19] A score of 1 or 2 is considered to be 'appropriate' and 3 or 4 as 'inappropriate' (Appendix, Supplementary Figure 1). For this study, individual prescription data were extracted for patients surveyed aged 0 days to less than 28 days of age where the indication group for antibiotic was recorded as "sepsis" and weight was recorded (to enable dose calculation). The principle unit of analysis was individual prescription. Dosing of gentamicin and benzylpenicillin was rounded to whole mg/kg. Year of survey was analysed by calendar year. We designated EOS by age criteria as sepsis indication for antibiotics with age <2 completed days. LOS was defined by age >=2 days at

antibiotic commencement or if age >7 days at audit date if antibiotic start date was missing. Prematurity was defined as gestational age<37 weeks. Dedicated children's hospitals, maternity hospitals or combined maternity/ children's hospitals were classed as specialist hospitals.

Ethics approval as a quality assurance project was obtained from the Melbourne Health Human Research Ethics Committee to coordinate the NAPS (No. QA2013066).

Patient involvement

Patients were not involved in the design or analysis of this study.

Statistical analysis

Categorical variables and proportions were summarized and compared between groups using a Chi-squared test. A P value of 0.05 (two-tailed) was deemed statistically significant. Dosing variability in mg/kg and antibiotic duration by groups was compared using Wilcoxon rank-sum tests. Statistical analyses and graphs were done using Stata 16.0 (StataCorp, College Station, TX, USA).

Results

Demographics

Among 884 neonatal prescriptions between 1 January 2014 and 31 December 2018, 415 prescriptions (46.9%) 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 prescriptions (44.3%) and the rest were for males. The number of prescriptions varied by year from 56 in 2014 to 91 in 2018. The majority of prescriptions were for neonates <7 days of age (342, 82.4%). Where this could be assessed, 71% of prescriptions (245/345) were for EOS and 29% (100/345) for LOS. Premature neonates accounted for 123 prescriptions (54.4%). The median weight was 2.9kg (IQR 1.9-3.4). Demographic details are shown in full in Table 1.

Antibiotic type and Duration

The Drug Utilization 90% (DU90): the number of antibiotics accounting for 90% of usage when ranked by frequency, included a total of 5 antibiotics. In descending order these were gentamicin, benzylpenicillin, cefotaxime, ampicillin and flucloxacillin. There were 323 (77.6%) prescriptions of either gentamicin or benzylpenicillin. One hundred and thirty-three neonates (62.1%) were prescribed both benzylpenicillin and gentamicin. Antibiotics most frequently prescribed are shown in Table 2 (complete list shown in Appendix Supplementary Table 1). At audit, 47.5% of antibiotics had been given for ≥2 days (Figure 1), though in only 15 prescriptions (3.6%) among 9 (4.2%) neonates, microbiologically confirmed infection was documented (Table 3). 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) (`Appendix, Supplementary Figure 2`) but did not differ by metropolitan versus rural hospital prescription.

Appropriateness and Guideline Compliance

Overall 400/415 prescriptions (96.4%) were assessed by local hospital auditors as appropriate and 13 (3.1%) inappropriate; with 330 prescriptions (79.5%) assessed as compliant with local

guidelines and 53 prescriptions (12.8%) as compliant with national *Therapeutic Guidelines*.[20] Nineteen prescriptions (4.6%) were assessed as non-compliant with guidelines. Detailed appropriateness and compliance assessment is displayed in Appendix, Supplementary Table 2. Appropriateness was similar for specialist and non-specialist hospitals (98% vs 95% appropriate) but guideline compliance was significantly higher in specialist hospitals (97.3% compared with 91.8%, respectively, P=0.013). Metropolitan hospitals had higher 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 2-8mg/kg (median 5mg/kg, IQR 4-5mg/kg). Gentamicin dose variability is shown in Figure 2a. Benzylpenicillin dosing and frequency information was available for 143 prescriptions. The dose varied 45-72mg/kg (median 60mg/kg, IQR 48-64). Benzylpenicillin dose variability is shown in Figure 2b. Dosing frequency also varied, though the majority of neonates received 24-hourly gentamicin and 12-hourly benzylpenicillin. Dosing for benzylpenicillin did not differ by hospital location (metropolitan versus 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. Auditor-assessed 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[21] and prescribing[22] 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.[21-24] Benzylpenicillin and gentamicin are recommended for empiric treatment of neonatal sepsis in current national guidelines[20] and are appropriate empiric therapy for the majority of organisms responsible for EOS in Australia.[7] This study confirms these are frequently used currently, though 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,[25] with potential long-term atopic and metabolic consequences of antibiotics in early life including asthma[26] and obesity.[27] Current challenges in standardizing 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.[28] 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 standardize and potentially improve care. A survey of 6 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 NICUs from 21 European countries, with 586 systemic antibiotic prescriptions for infants up to 90 days of age, reported a tendency to over-dosing of penicillins and under-dosing of vancomycin and gentamicin, relative to guidelines.[29] Although we found variation both above and below recommended doses for benzylpenicillin and gentamicin in neonates treated for sepsis, we also found a tendency to underdosing of 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 grams at ≤ 5%.[30] Relative to body size, this phenomenon accounts for additional variation not seen in the adult population, where standardized 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,[31] national guidelines for neonatal sepsis prescribing did not exist during the period of this study. These are now available, however, with national *Therapeutic Guidelines*[20] 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 Formulary (ANMF) group. The ANMF group provides freely available, evidence-based and regularly updated medicine guidelines for neonates.[32] Both the Australasian Neonatal Medicines Formulary (ANMF)[32] and *Therapeutic Guidelines*[20] recommend dosing of 5mg/kg for gentamicin and 60mg/kg for benzylpenicillin (90mg/kg for meningitis), with frequency dependent on gestational and postnatal age. These may serve as references for future assessment of neonatal sepsis prescribing as national standard recommendations.

On audit date, almost 50% of antibiotics had been given for 2 or more completed days, though only 4% of neonates had microbiologically confirmed infection documented. This may represent excessive antibiotic therapy and provides an opportunity for quality improvement, given that the majority of potential pathogens in neonatal sepsis are identified within 36-48 hours.[33] Hospital antimicrobial stewardship teams may not include neonatal pharmacologists 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 of prescribing, particularly with regard to dosing in sepsis therapy, should be possible.

Over 95% of therapy for neonatal sepsis was deemed appropriate by local assessors and over 90% deemed compliant with guidelines in this study. This is similar to a previous Australian study in which only 4% of prescriptions were considered inappropriate.[22] Compliance was also deemed high in this study, largely based on compliance with local guidelines. Although

12.8% of prescriptions were reported as compliant with *Therapeutic Guidelines*, these specifically excluded recommendations for neonates at the time of this study. Given the substantial dosing variation and potentially excessive durations described above, these findings suggest challenges with local assessment of appropriateness and guideline compliance of therapy for sepsis in neonates. It is difficult to say whether the degree of variation in prescribing demonstrated here led to suboptimal outcomes. Nonetheless, we question whether such diversity in dosing for a handful of well-known drugs can be said to be optimal therapy.

In this study we were unable to compare prescribing with local guidelines used within each hospital, and this is a substantial limitation, though it reinforces our point that diversity of guidelines is a major challenge to achieving standardized prescribing. We also do not currently have information on the proportion of neonates in each hospital who were not prescribed antibiotics. Weight was not a mandatory field in the NAPS tool at 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 children. The data here may not be applicable to countries with high rates of drug-resistant organisms causing neonatal sepsis[12,34] 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 is in keeping with available national data showing relatively low rates of drug-resistant pathogens in neonatal sepsis.[35]

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. 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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Transparency Declaration

All authors declare that they have no competing interests, financial or otherwise.

Contributorship statement

BM planned and conducted the study, reviewed the data and co-wrote the manuscript, submitted the study and is responsible for overall content. CC reviewed the data and co-wrote the manuscript. NS planned the study, reviewed the data and co-wrote the manuscript. RJ reviewed the data and co-wrote the manuscript. CJ reviewed the data and co-wrote the manuscript. PK reviewed the data and co-wrote the manuscript. CB reviewed the data and co-wrote the manuscript. KT planned the study, reviewed the data and co-wrote the manuscript.

What is already known on this topic

(a maximum of 3 brief statements (no more than 25 words per statement)

- Neonatal sepsis is an important cause of morbidity and mortality globally
- There is considerable uncertainty about antibiotic prescribing and optimal regimens to treat neonatal sepsis
- Current challenges include lack of epidemiological data to inform prescribing improvements

What this study adds

(a maximum of 3 brief statements (no more than 25 words per statement)

- Benzylpenicillin and gentamicin accounted for more than three quarters of antibiotics prescribed for sepsis among Australian neonates, only 4% of whom had microbiologically confirmed infection.
- There was considerable variation in dosing for both benzylpenicillin and gentamicin
- There is an opportunity to improve prescribing and reduce unnecessary variation by targeting a small number of drugs in the treatment of neonatal sepsis

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Figures and Tables

Table 1: Demographic Details

DEMOGRAPHIC	Total prescriptions (415)	(%)
Gestational age		
<25 weeks	20	4.8%
25-<30 weeks	32	7.7%
30-<35 weeks	52	12.5%
35-<37 weeks	21	5.1%
>=37 weeks	101	24.3%
(not stated)	*189*	*45.5%*
Postnatal age		
<7 days	342	82.4%
7-<15 days	38	9.2%
15-<28 days	35	8.4%
Sex: Female	184	44.3%
Median weight in kg (IQR)	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

Table 2: Top 5 Antibiotics by Frequency Prescribed and Sepsis Type

Antibiotic: All	**Prescriptions Total 415 n (%)**	**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
Antibiotic: EOS*	**Prescriptions Total 245 n (%)**	**Cumulative Percentage**
Gentamicin	119 (48.6)	48.6
Benzylpenicillin (Penicillin G)	100 (40.8)	89.4
Ampicillin	12 (4.9)	94.3
Amoxicillin	5 (2)	96.3
Benzathine penicillin	3 (1.2)	97.6
Antibiotic: LOS*	**Prescriptions Total 100 n (%)**	**Cumulative Percentage**
Gentamicin	31 (31)	31
Cefotaxime	18 (18)	49
Benzylpenicillin (Penicillin G)	16 (16)	65
Vancomycin	11 (11)	76
Flucloxacillin	10 (10)	86

*EOS=early-onset sepsis; LOS=late-onset sepsis

Table 3 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)

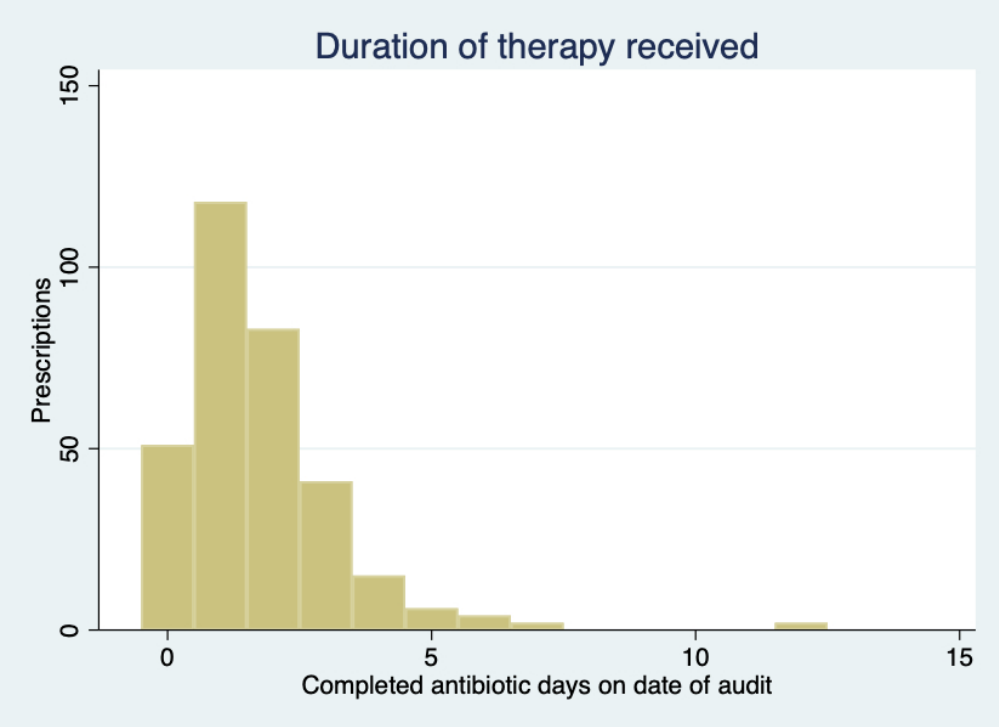
*One infant had *Candida glabrata* and coagulase-negative *Staphylococcus* in blood cultures and was treated with liposomal Amphotericin B. The other had *Candida albicans* in blood culture. This infant was treated with fluconazole for indication "candidaemia" and benzylpenicillin and cefotaxime for indication "sepsis".

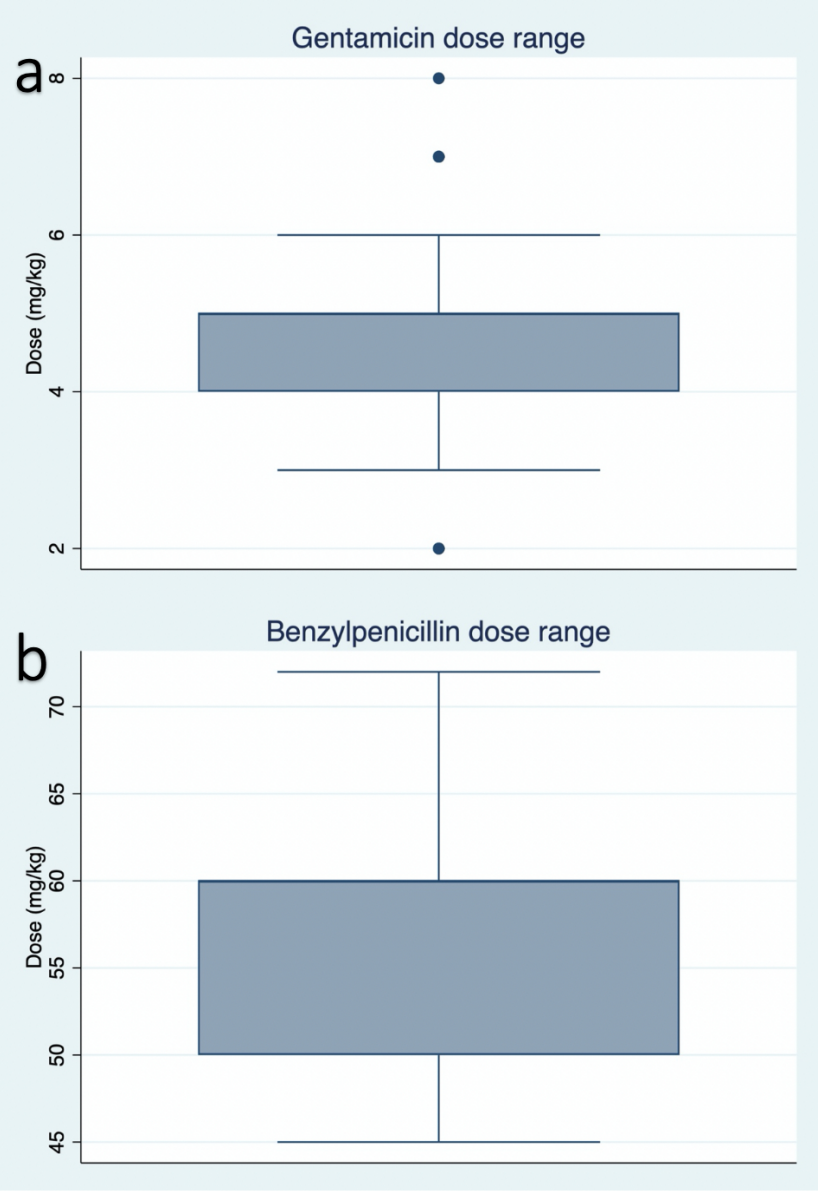
**One infant had gram-positive cocci detected in blood culture, awaiting species confirmation at time of audit, the other had pneumonia with *Klebsiella oxytoca* isolated from endotracheal tube aspirate culture

Figure 1: Duration of therapy (completed antibiotic days at audit date)

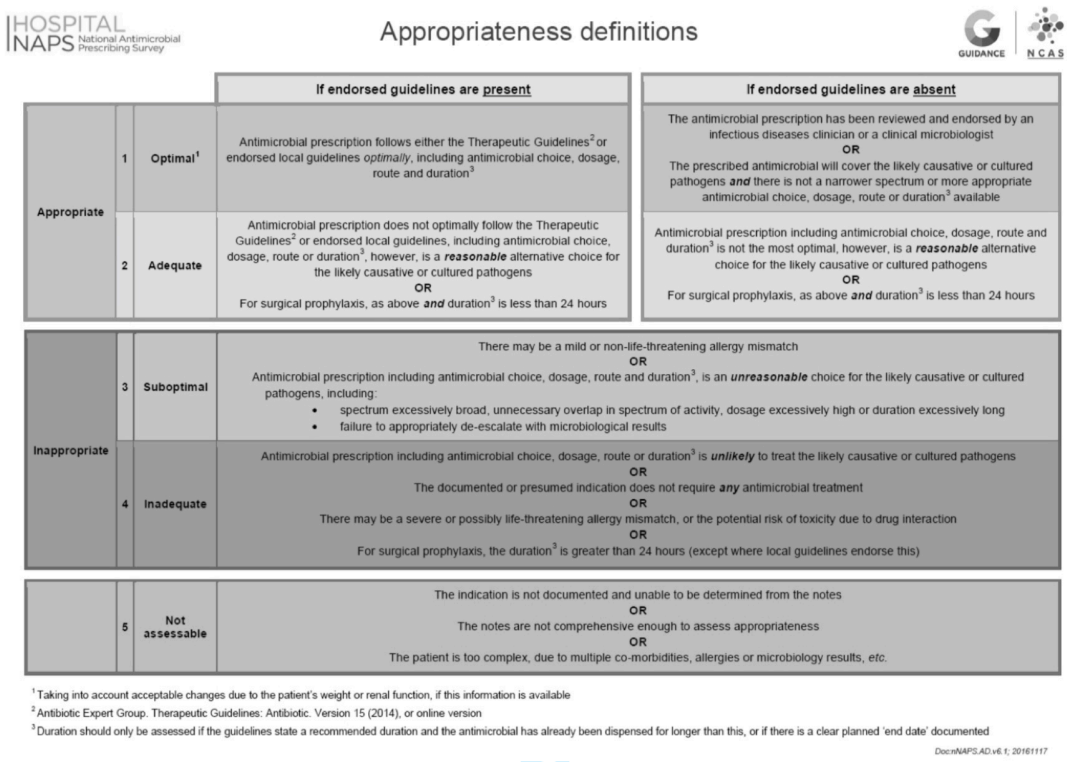
Figure 2: Individual dose ranges for gentamicin and benzylpenicillin (whole mg/kg)

*2a, Gentamicin (n=178) One 52mg/kg dose omitted from table, as apparent 10-fold error
*2b, Benzylpenicillin (n=143) One 6mg/kg dose omitted from figure, as apparent 10-fold error


Duration of therapy received
Prescriptions
0
50
100
150
0
5
10
15
Completed antibiotic days on date of audit


Gentamicin dose range
a
Dose (mg/kg)
2
4
6
8
Benzylpenicillin dose range
b
Dose (mg/kg)
45
50
55
60
65
70

Appendix: Supplementary Material



Supplementary Figure 1: Definitions of appropriate prescribing

Supplementary Table 1: Antibiotics by Frequency Prescribed

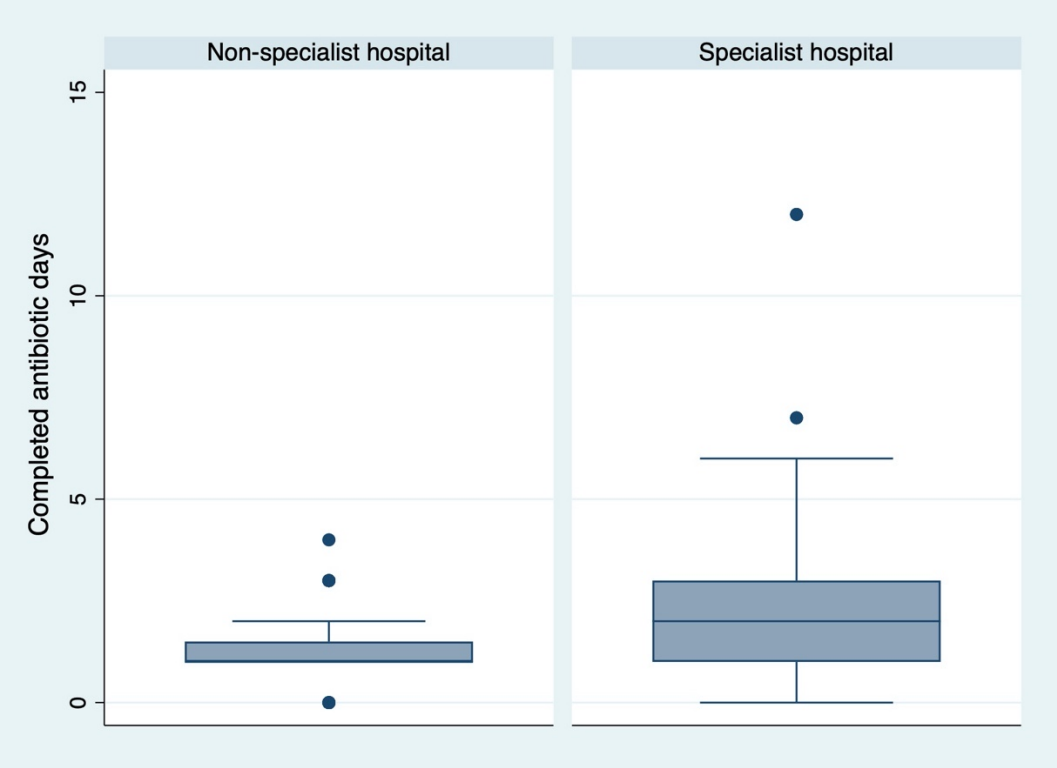
Antibiotic	Prescriptions*	Percentage	Cumulative Percentage
Gentamicin	179	43.1	43.1
Benzylpenicillin (Penicillin G)	144	34.7	77.8
Cefotaxime	26	6.3	84.1
Ampicillin	18	4.3	88.4
Flucloxacillin	13	3.1	91.6
Vancomycin	13	3.1	94.7
Amoxicillin (Amoxycillin)	9	2.2	96.9
Meropenem	6	1.45	98.3
Benzathine penicillin	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

Supplementary Table 2: Antibiotic Appropriateness and Compliance with Guidelines

Appropriateness*	**Frequency****	**Percentage**
1-Optimal	373	89.9
2-Adequate	27	6.5
3-Suboptimal	11	2.7
4-Inadequate	2	0.5
5-Not Assessable	2	0.5
Compliance with Guidelines*	**Frequency****	**Percentage**
Compliant with locally endorsed guidelines	330	79.5
Compliant with *Therapeutic Guidelines*	53	12.8
Non-compliant with guidelines	19	4.6
Directed therapy	7	1.7
No guidelines available	4	1
Not assessable	2	0.5

*These are assessed by trained local auditors and categories are mutually exclusive
**N=415 prescriptions



Supplementary Figure 2: Antibiotic duration by specialist and non-specialist hospital

Antibiotic duration in specialist hospitals: median 2 days (IQR 1-3 days), in non-specialist hospitals median 1 day (IQR 1-1.5 days), P<0.0001.

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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 hospitalized neonates, using the National Antimicrobial Prescribing Survey (NAPS) 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 2mg/kg to 8mg/kg for gentamicin (median 5mg/kg, IQR 4-5mg/kg) and 45-72mg/kg for benzylpenicillin (median 60mg/kg, IQR 50-60) though only 13 (3.2%) and 19 (4.6%) of 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, though microbiologically confirmed infection was documented in only 9 neonates (4.2%).

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,[1] 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 immunologic 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-specific,[5] thus empiric antibiotic therapy is commonly prescribed for hospitalized 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 recognized, 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.[10] This only applies to neonates with early-onset sepsis, however, and similar tools for late-onset sepsis are lacking.

In recognition that epidemiology of sepsis in neonates varies with age, it is commonly divided into early-onset sepsis (EOS) and late-onset sepsis (LOS). While risk and microbiology of sepsis in the first few days of life is 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 post-natal environment, though the utility of this division across global

settings has been challenged.[11] 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).[12] Common pathogens identified in EOS have been better characterised than those causing LOS in Australia, though both have been described in the United Kingdom.[6,13]

In this study we aimed to report on antimicrobial prescribing for neonatal sepsis of all types, using a national dataset 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 NAPS database of point-prevalence prescribing surveys for Australian hospitals from all 6 Australian states and 2 territories (1 January 2014 to 31 December 2018).[14] Participation in these surveys is voluntary and data are submitted through a web-based interface to a central database.[14] Hospitals can participate in these surveys whenever they choose though most participate annually. Survey methodology has been described previously;[15,16]in brief, the dataset 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 hospital, network or regional guidelines, other than the nationally used Therapeutic Guidelines.[17] Assessors can choose to select from various potential reasons for inappropriate prescribing, including "spectrum too broad", "spectrum too narrow", "incorrect route", "incorrect dose or frequency", "incorrect duration",

"allergy mismatch" or "microbiology mismatch"; these are not mutually exclusive. Appropriateness assessments were conducted by trained local surveyors as described previously[18,19] A score of 1 or 2 is considered to be 'appropriate' and 3 or 4 as 'inappropriate' (Appendix, Supplementary Figure 1). For this study, individual prescription data were extracted for patients surveyed aged 0 days to less than 28 days of age where the indication group for antibiotic was recorded as "sepsis" and weight was recorded (to enable dose calculation). The principle unit of analysis was individual prescription. Dosing of gentamicin and benzylpenicillin was rounded to whole mg/kg. Year of survey was analysed by calendar year. We designated EOS by age criteria as sepsis indication for antibiotics with age <2 completed days. LOS was defined by age >=2 days at antibiotic commencement or if age >7 days at audit date if antibiotic start date was missing. Prematurity was defined as gestational age<37 weeks. Dedicated children's hospitals, maternity hospitals or combined maternity/children's hospitals were classed as specialist hospitals.

Ethics approval as a quality assurance project was obtained from the Melbourne Health Human Research Ethics Committee to coordinate the NAPS (No. QA2013066).

Patient involvement

Patients were not involved in the design or analysis of this study.

Statistical analysis

Categorical variables and proportions were summarized and compared between groups using a Chi-squared test. A P value of 0.05 (two-tailed) was deemed statistically significant. Dosing variability in mg/kg and antibiotic duration by groups was compared using Wilcoxon rank-

sum tests. Statistical analyses and graphs were done using Stata 16.0 (StataCorp, College Station, TX, USA).

Results

Demographics

Among 884 neonatal prescriptions between 1 January 2014 and 31 December 2018, 415 prescriptions (46.9%) 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 prescriptions (44.3%) and the rest were for males. 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% of prescriptions (245/345) were for EOS and 29% (100/345) for LOS. Premature neonates accounted for 123 prescriptions (54.4% of prescriptions for which gestational age was available). The median weight was 2.9kg (IQR 1.9-3.4). Demographic details are shown in full in Table 1.

Antibiotic type and Duration

The Drug Utilization 90% (DU90): the number of antibiotics accounting for 90% of usage when ranked by frequency, included a total of 5 antibiotics. In descending order these were gentamicin, benzylpenicillin, cefotaxime, ampicillin and flucloxacillin. Twenty neonates (9.3%) were prescribed one antimicrobial for sepsis, 187 neonates (87.4%) 2 antimicrobials and 7 neonates (3.3%) 3 antimicrobials. There were 323 (77.8%) prescriptions of either

gentamicin or benzylpenicillin and 133/214 neonates (62.1%) 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 prescriptions (3.6%) 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) (Appendix, Supplementary Figure 2) but did not differ by metropolitan versus rural hospital prescription.

Appropriateness and Guideline Compliance

Overall 400/415 prescriptions (96.4%) were assessed by local hospital auditors as appropriate and 13 (3.1%) inappropriate; with 330 prescriptions (79.5%) assessed as compliant with local guidelines and 53 prescriptions (12.8%) as compliant with national *Therapeutic Guidelines.*[20] Nineteen prescriptions (4.6%) were assessed as non-compliant with guidelines. Detailed appropriateness and compliance assessment is displayed in Appendix, Supplementary 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 2-8mg/kg (median 5mg/kg, IQR 4-5mg/kg). Gentamicin dose variability is

shown in Figure 2a. Benzylpenicillin dosing and frequency information was available for 143 prescriptions. The dose varied 45-72mg/kg (median 60mg/kg, IQR 50-60) and benzylpenicillin dose variability is shown in Figure 2b. Dosing frequency also varied, though the majority of neonates received 24-hourly gentamicin and 12-hourly benzylpenicillin (Appendix, Supplementary Table 2). Dosing for benzylpenicillin did not differ by hospital location (metropolitan versus 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 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[21] and prescribing[22] 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.[21-24] Benzylpenicillin and gentamicin are recommended for empiric treatment of neonatal sepsis in current national guidelines[20] and are appropriate empiric therapy for the majority of organisms responsible for EOS in Australia.[6] This study confirms these are frequently used currently, though 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,[25] with potential long-term atopic and metabolic consequences of antibiotics in early life including asthma[26] and obesity.[27] 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 standardizing 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 standardize and potentially improve care. A survey of 6 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 NICUs from 21 European countries, with 586 systemic antibiotic prescriptions for infants up

to 90 days of age, reported a tendency to over-dosing of penicillins and under-dosing of 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 to underdosing of 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 grams at ≤ 5%.[31] Relative to body size, this phenomenon accounts for additional variation not seen in the adult population, where standardized 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*[20] 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 Formulary (ANMF) group. The ANMF group provides freely available, evidence-based and regularly updated medicine guidelines for neonates.[33] Both the Australasian Neonatal Medicines Formulary (ANMF)[33] and *Therapeutic Guidelines*[20] recommend dosing of 5mg/kg for gentamicin and 60mg/kg for benzylpenicillin (90mg/kg for meningitis), with frequency dependent on gestational and postnatal age. These may serve as

references 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, though 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,[34] this may represent excessive antibiotic therapy and provides an opportunity for quality improvement. Hospital antimicrobial stewardship teams may not include neonatal pharmacologists 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 of prescribing, particularly with regard to dosing in sepsis therapy, should be possible.

Over 95% of therapy for neonatal sepsis was deemed appropriate by local assessors and over 90% deemed compliant with guidelines in this study. This is similar to a previous Australian study in which only 4% of prescriptions were considered inappropriate.[22] Compliance was also deemed high in this study, largely based on compliance with local guidelines. Although 12.8% of prescriptions were reported as compliant with *Therapeutic Guidelines*, these specifically excluded recommendations for neonates at the time of this study. Given the substantial dosing variation and potentially excessive durations described above, these findings suggest challenges with local assessment of appropriateness and guideline compliance of therapy for sepsis in neonates. It is difficult to say whether the degree of variation in prescribing demonstrated here led to suboptimal outcomes. Nonetheless, we question whether such diversity in dosing for a handful of well-known drugs can be said to be optimal therapy.

In this study we were unable to compare prescribing with local guidelines used within each hospital, and this is a substantial limitation, though it reinforces our point that diversity of guidelines is a major challenge to achieving standardized prescribing. In addition to this, as we have described above, it is possible that compliance and appropriateness have been over-attributed by local assessors, though this may in future be ameliorated by new national guidelines and further assessor training. We also do not currently have information on the proportion of neonates in each hospital who were not prescribed antibiotics. Weight was not a mandatory field in the NAPS tool at 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 children. 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[11,35] 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 is in keeping with available national data showing relatively low rates of drug-resistant pathogens in neonatal sepsis.[36]

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 infection. 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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Transparency Declaration

All authors declare that they have no competing interests, financial or otherwise.

Contributorship statement

BM planned and conducted the study, reviewed the data and co-wrote the manuscript, submitted the study and is responsible for overall content. CC reviewed the data and co-wrote the manuscript. NS planned the study, reviewed the data and co-wrote the manuscript. RJ reviewed the data and co-wrote the manuscript. CJ reviewed the data and co-wrote the manuscript. PK reviewed the data and co-wrote the manuscript. CB reviewed the data and co-wrote the manuscript. KT planned the study, reviewed the data and co-wrote the manuscript.

What is already known on this topic

(a maximum of 3 brief statements (no more than 25 words per statement)

- Neonatal sepsis is an important cause of morbidity and mortality globally
- There is considerable uncertainty about antibiotic prescribing and optimal regimens to treat neonatal sepsis
- Current challenges include lack of epidemiological data to inform prescribing improvements

What this study adds

(a maximum of 3 brief statements (no more than 25 words per statement)

- Benzylpenicillin and gentamicin accounted for more than three quarters of antibiotics prescribed for sepsis among Australian neonates, only 4% of whom had microbiologically confirmed infection.
- There was considerable variation in dosing for both benzylpenicillin and gentamicin
- There is an opportunity to improve prescribing and reduce unnecessary variation by targeting a small number of drugs in the treatment of neonatal sepsis

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Figures and Tables

Table 1: Demographic Details

DEMOGRAPHIC	Total prescriptions (415)	(%)
Gestational age		
<25 weeks	20	4.8%
25-<30 weeks	32	7.7%
30-<35 weeks	52	12.5%
35-<37 weeks	21	5.1%
>=37 weeks	101	24.3%
(not stated)	*189*	*45.5%*
Postnatal age		
<7 days	342	82.4%
7-<15 days	38	9.2%
15-<28 days	35	8.4%
Sex: Female	184	44.3%
Median weight in kg (IQR)	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

Table 2: Antibiotics by Frequency Prescribed

Antibiotic	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 Total 415 n (%)**	**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
Antibiotic: EOS*	**Prescriptions Total 245 n (%)**	**Cumulative Percentage**
Gentamicin	119 (48.6)	48.6
Benzylpenicillin (Penicillin G)	100 (40.8)	89.4
Ampicillin	12 (4.9)	94.3
Amoxicillin	5 (2)	96.3
Benzathine penicillin	3 (1.2)	97.6
Antibiotic: LOS*	**Prescriptions Total 100 n (%)**	**Cumulative Percentage**
Gentamicin	31 (31)	31
Cefotaxime	18 (18)	49
Benzylpenicillin (Penicillin G)	16 (16)	65
Vancomycin	11 (11)	76
Flucloxacillin	10 (10)	86

*EOS=early-onset sepsis; LOS=late-onset sepsis

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 *Candida albicans* in blood culture. This infant was treated with fluconazole for indication "candidaemia" and benzylpenicillin and cefotaxime for indication "sepsis".

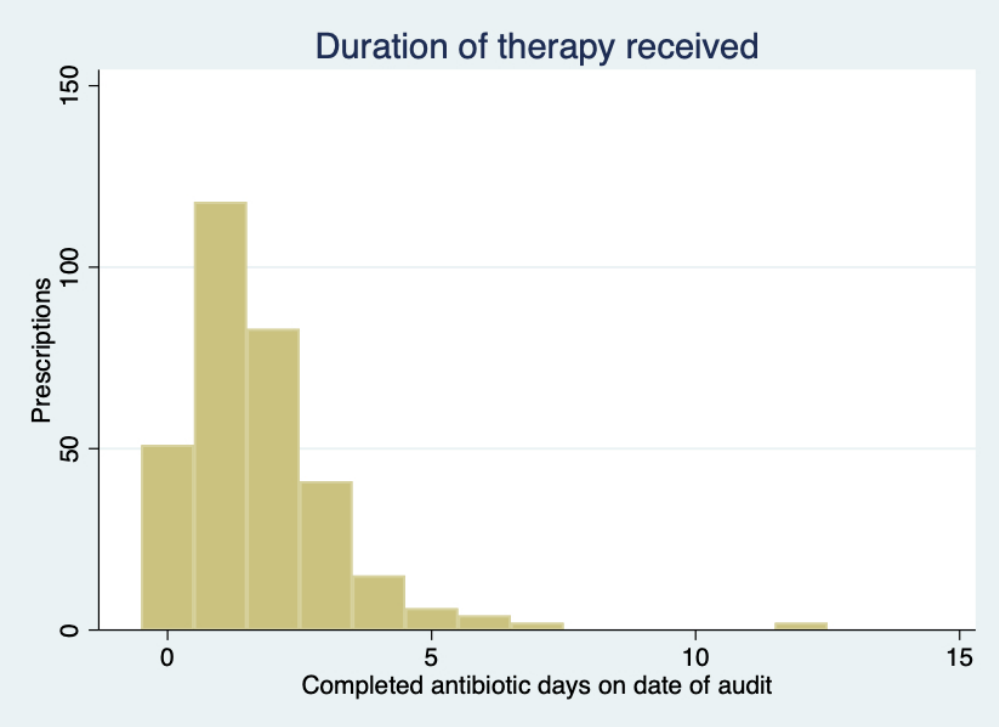
**One infant had gram-positive cocci detected in blood culture, awaiting species confirmation at time of audit, the other had pneumonia with *Klebsiella oxytoca* isolated from endotracheal tube aspirate culture

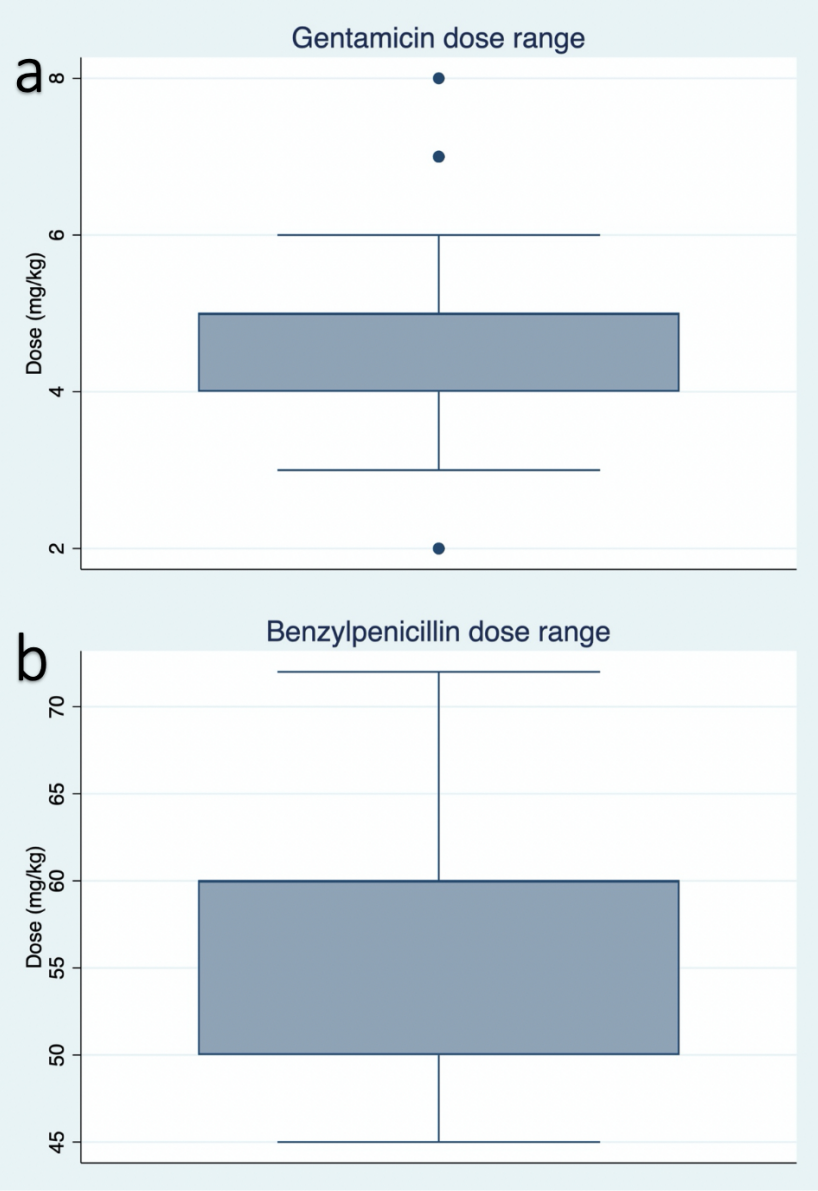
***Only one infant with microbiologically confirmed infection met criteria for EOS, with as yet unidentified gram-positive cocci in blood culture.

Figure 1: Duration of therapy (completed antibiotic days at audit date)

Figure 2: Individual dose ranges for gentamicin and benzylpenicillin (whole mg/kg)

*2a, Gentamicin (n=178) Median gentamicin dose 5mg/kg, IQR 4-5mg/kg, dots represent outliers; one 52mg/kg dose omitted from table, as apparent 10-fold error
*2b, Benzylpenicillin (n=143) Median benzylpenicillin dose 60mg/kg, IQR 50-60; one 6mg/kg dose omitted from figure, as apparent 10-fold error


Duration of therapy received
Prescriptions
0
50
100
150
0
5
10
15
Completed antibiotic days on date of audit


Gentamicin dose range
a
Dose (mg/kg)
2
4
6
8
Benzylpenicillin dose range
b
Dose (mg/kg)
45
50
55
60
65
70

Appendix: Supplementary Material

HOSPITAL NAPS National Antimicrobial Prescribing Survey

Appropriateness definitions

GUIDANCE | NCAS

			If endorsed guidelines are present	If endorsed guidelines are absent
Appropriate	1	Optimal[1]	Antimicrobial prescription follows either the Therapeutic Guidelines[2] or endorsed local guidelines *optimally*, including antimicrobial choice, dosage, route and duration[3]	The antimicrobial prescription has been reviewed and endorsed by an infectious diseases clinician or a clinical microbiologist **OR** The prescribed antimicrobial will cover the likely causative or cultured pathogens ***and*** there is not a narrower spectrum or more appropriate antimicrobial choice, dosage, route or duration[3] available
	2	Adequate	Antimicrobial prescription does not optimally follow the Therapeutic Guidelines[2] or endorsed local guidelines, including antimicrobial choice, dosage, route or duration[3], however, is a ***reasonable*** alternative choice for the likely causative or cultured pathogens **OR** For surgical prophylaxis, as above ***and*** duration[3] is less than 24 hours	Antimicrobial prescription including antimicrobial choice, dosage, route and duration[3] is not the most optimal, however, is a ***reasonable*** alternative choice for the likely causative or cultured pathogens **OR** For surgical prophylaxis, as above ***and*** duration[3] is less than 24 hours
Inappropriate	3	Suboptimal	There may be a mild or non-life-threatening allergy mismatch **OR** Antimicrobial prescription including antimicrobial choice, dosage, route and duration[3], is an ***unreasonable*** choice for the likely causative or cultured pathogens, including: • spectrum excessively broad, unnecessary overlap in spectrum of activity, dosage excessively high or duration excessively long • failure to appropriately de-escalate with microbiological results	
	4	Inadequate	Antimicrobial prescription including antimicrobial choice, dosage, route or duration[3] is ***unlikely*** to treat the likely causative or cultured pathogens **OR** The documented or presumed indication does not require ***any*** antimicrobial treatment **OR** There may be a severe or possibly life-threatening allergy mismatch, or the potential risk of toxicity due to drug interaction **OR** For surgical prophylaxis, the duration[3] is greater than 24 hours (except where local guidelines endorse this)	
	5	Not assessable	The indication is not documented and unable to be determined from the notes **OR** The notes are not comprehensive enough to assess appropriateness **OR** The patient is too complex, due to multiple co-morbidities, allergies or microbiology results, *etc.*	

[1] Taking into account acceptable changes due to the patient's weight or renal function, if this information is available

[2] Antibiotic Expert Group. Therapeutic Guidelines: Antibiotic. Version 15 (2014), or online version

[3] Duration should only be assessed if the guidelines state a recommended duration and the antimicrobial has already been dispensed for longer than this, or if there is a clear planned 'end date' documented

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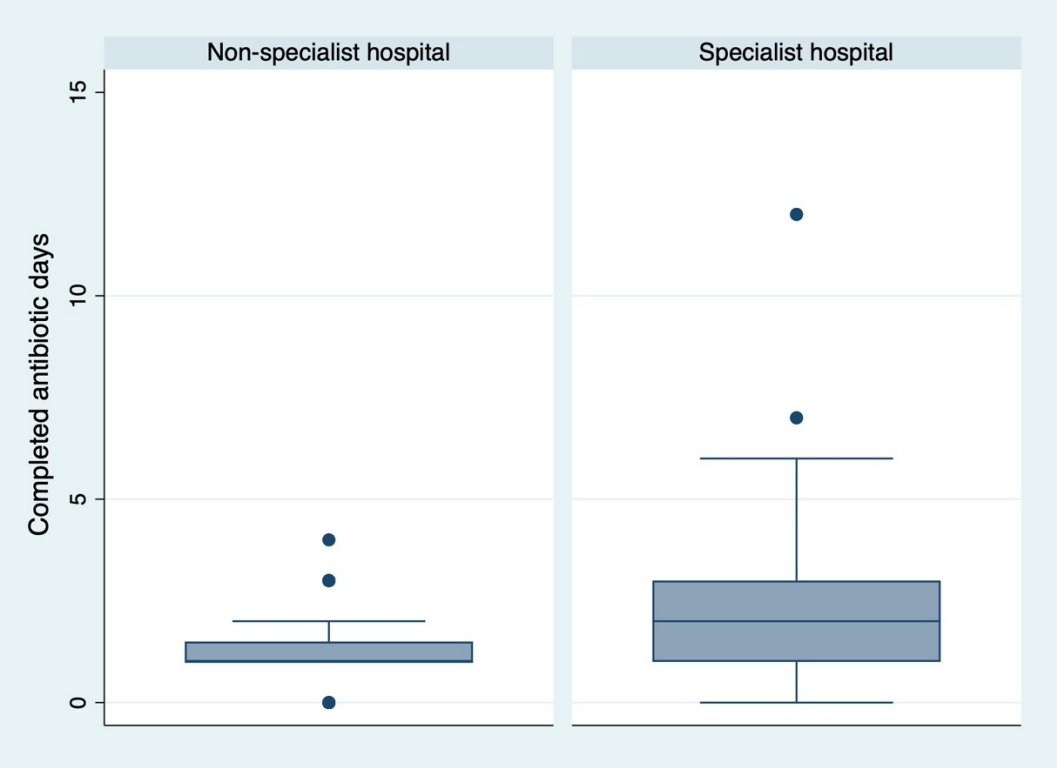
Supplementary Figure 1: Definitions of appropriate prescribing

Supplementary Table 1: Antibiotic Appropriateness and Compliance with Guidelines

Appropriateness*	**Frequency****	**Percentage**
1-Optimal	373	89.9
2-Adequate	27	6.5
3-Suboptimal	11	2.7
4-Inadequate	2	0.5
5-Not Assessable	2	0.5
Compliance with Guidelines*	**Frequency****	**Percentage**
Compliant with locally endorsed guidelines	330	79.5
Compliant with *Therapeutic Guidelines*	53	12.8
Non-compliant with guidelines	19	4.6
Directed therapy	7	1.7
No guidelines available	4	1
Not assessable	2	0.5

*These are as assessed by trained local auditors and categories are mutually exclusive
**N=415 prescriptions



Supplementary Figure 2: Antibiotic duration by specialist and non-specialist hospital

Antibiotic duration in specialist hospitals: median 2 days (IQR 1-3 days), in non-specialist hospitals median 1 day (IQR 1-1.5 days), P<0.0001. Dots represent outliers.

Supplementary Table 2: Dosing Frequency for Gentamicin and Benzylpenicillin

Gentamicin	Frequency	Percentage
24-hourly	100	55.9
36-hourly	43	24
48-hourly	26	14.5
Single dose	10	5.6
Total	179	100
Benzylpenicillin	Frequency	Percentage
12-hourly	141	97.9
8-hourly	3	2.1
Total	144	100