**Title Page**

Title: Antimicrobial Resistance in UK Neonatal Units: neonIN Infection Surveillance Network

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On behalf of the neonIN network

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**Contributorship Statement:**

BC and CK contributed to the design of the analysis, conducted the analysis of the data, drafted the manuscript and revised it according to feedback from co-authors.

PH developed the neonIN network, designed the current analysis and provided critical appraisal as well as final approval of the manuscript.

JB, SP, AG, JM, AB and NK made substantial contributions to the acquisition of data for the analysis, critically revised the manuscript and provided final approval for the version to be submitted.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Abstract**

**Objective:**

To define the susceptibilities of the common causative pathogens of neonatal sepsis in the UK.

**Design:**

Retrospective analysis of the prospectively collected neonIN infection surveillance network data between 2005 and 2014.

**Setting:**

30 neonatal units in the United Kingdom.

**Patients:**

Newborns admitted to participating neonatal units who return a positive blood, cerebrospinal fluid or urine culture and are treated with at least five days of appropriate antibiotics.

**Results:**

1,568 isolates with recorded antimicrobial data were collected including 328 early onset sepsis (EOS) isolates and 1,240 late onset (LOS) isolates. The majority of EOS pathogens (>92%) were susceptible to the four empiric commonly used antimicrobial combinations (e.g. 93% for benzylpenicillin/gentamicin), while LOS pathogens demonstrated higher levels of resistance (e.g. 89% for flucloxacillin/gentamicin). Among infants <1500g and <32 weeks gestation an amoxicillin/gentamicin combination demonstrated a trend towards improved coverage of EOS isolates than benzylpenicillin/gentamicin (93% vs. 86%, p=0.211).

**Conclusions:**

This analysis provides insights into the patterns of antimicrobial resistance among UK neonatal pathogens. These data will inform areas of future research and can be used to update national evidence-based guidelines on antimicrobial usage.

**Introduction:**

Newborn babies are at a significant risk of infection during the neonatal period, especially those born prematurely or of low birth-weight.(1) Neonatal infection is associated with considerable morbidity and mortality, being responsible for more than 250 neonatal deaths each year in the UK alone.(2-4) Infection during the neonatal period is classically divided into two distinct clinical syndromes based on the likely causative pathogens: early-onset sepsis (EOS) and late-onset sepsis (LOS).(4,5)

The presentation of neonatal sepsis is typically non-specific and empiric antimicrobial treatment is generally commenced before a causative organism is identified and targeted therapy can be initiated.(6) It is therefore crucial to have a thorough understanding of the current epidemiology of neonatal infections in order to select the most effective and appropriate antibiotic combinations for empiric treatment.(5)

The development and spread of antimicrobial resistance is now a major challenge in modern medicine, emphasizing the importance of using antimicrobial agents appropriately and rationally (7-9) There are now growing concerns that empiric treatment is increasingly likely to be inadequate in terms of antibiotic cover, especially in settings where there is a high prevalence of antimicrobial resistance. For example, recent modelling puts neonatal deaths due to resistant organisms in China, India, Pakistan, Nigeria and the Democratic Republic of Congo alone at 215,000 per year. (10)

neonIN (www.neonin.org.uk) is a neonatal infection surveillance network established in 2004 with the aim of collecting and storing information about the causative pathogens of neonatal infection and their antimicrobial susceptibility patterns. Similar surveillance networks have been successfully implemented in other countries and have provided valuable insights into the longitudinal epidemiology of infections and effectiveness of empiric antibiotic prescribing guidelines.(11,12,13)

The objective of this analysis was to define the susceptibilities of the common causative pathogens of neonatal sepsis in the UK and to provide guidance on empiric antimicrobial combinations. The epidemiology of infections in the neonIN network has been reported elsewhere.

**Methods:**

neonIN collects data on all episodes of neonatal infection in participating neonatal units. An episode of neonatal infection is defined as a positive culture collected from the blood, cerebrospinal fluid (CSF) or urine (obtained via sterile technique), for which clinicians prescribed at least five days of appropriate antibiotics. Data are collected using a standardised online questionnaire which is completed by the clinician for each positive culture result.

Repeatedly positive samples are considered to represent the same episode of infection unless they occurred more than seven days after the last positive culture result. EOS is defined as infection occurring less than 48 hours after birth while episodes thereafter are classified as LOS. This age cut-off was chosen as it most likely represents the transition between pathogens which are acquired via vertical and horizontal transmission, however an analysis based on a 72 hours cut-off was also performed.

Antimicrobial susceptibility data were analysed against a pre-defined list of commonly used empiric antimicrobial combinations including those recommended by the British National Formulary for Children (BNFC), and the National Institute for Health and Care Excellence (NICE) EOS antibiotic guidelines (Table 1).(14,15) These choices are also consistent with the findings of a review of antimicrobial policies in use in UK neonatal units in 2008.(16)

*Insert Table 1 Here*

Organisms were deemed ‘susceptible’ if susceptible to at least one of the antibiotics in the combination and ‘resistant’ if resistant to all the constituent antibiotics individually. The exception to this occurred in cases where monotherapy was deemed to be inappropriate (e.g. if an enterococcus isolate was recorded as ‘susceptible’ to gentamicin and there was no susceptibility data for flucloxacillin, then the culture was not listed as sensitive to the combination, as enterococci are intrinsically resistant to gentamicin). Otherwise, if susceptibility data were only available for one of the antimicrobial agents in the combination then the pathogen was labelled as per the susceptibility of the antibiotic tested.

Data were extracted from the online neonIN database and imported into Stata 14 for analysis. Statistical significance was defined as a p-value of <0.05. Two methods were chosen to define the confidence of coverage estimates. Firstly, 95% confidence intervals were calculated for each coverage estimate and secondly, best and worst-case scenarios were calculated by classifying all isolates without complete antimicrobial resistance profiles as either sensitive or resistant respectively. Finally, in recognition of the fact that antimicrobial susceptibilities may change over time, we conducted a further analysis of the data by comparing the two five-year time-periods: 2005-2009 and 2010-2014.

The neonIN database received ethics approval from the London-Surrey Borders Research Ethics Committee in April 2005 (05/Q0806/34) and again in December 2013 (05/Q0806/34+5).

**Results:**

Data were extracted for the 10 years between 1 January 2005 and 31 December 2014. The number of UK units contributing to neonIN increased each year between 2005 and 2014: 5, 8, 9, 12, 14, 16, 20, 24, 29 and 30.

For 1,568 of the 2,667 isolates (59%), data were available on antimicrobial susceptibilities. Of these, 328 isolates represented EOS (62% of all EOS isolates) and 1,240 LOS (58% of all LOS isolates). The vast majority of recorded isolates were blood cultures (91.3%), with urine obtained via sterile technique (4.9%) and CSF (2.2%) the other common sources. There were no significant differences between isolates for which susceptibility data were available and those for which they were not with regard to patient demographics (birth-weight, gestational age or post-natal age) (p>0.3 for all). Isolates were statistically significantly more likely to have a complete susceptibility profile if they were from blood cultures (Supplementary Table 1).

Antibiotic susceptibilities to empiric combinations

The majority of EOS pathogens (>92%) were susceptible to the four empiric antimicrobial combinations tested. Cefotaxime monotherapy demonstrated a susceptibility rate of 98%. The BNFC combinations of benzylpenicillin and gentamicin or amoxicillin and cefotaxime demonstrated rates of 93% and 95% respectively (Table 2).(14) There was a statistically significant difference in the coverage of benzylpenicillin and gentamicin in comparison to cefotaxime monotherapy (p=0.037), but not for the other combinations.

LOS pathogens demonstrated higher levels of resistance than EOS pathogens. A combination of vancomycin and cefotaxime displayed coverage of 92% of isolates tested while flucloxacillin and gentamicin covered 89% (Table 2).(14) Amoxicillin and clavulanic acid provided significantly lower coverage than any other tested combination (p<0.02), while flucloxacillin and gentamicin was notably more effective as a combination for LOS than amoxicillin and cefotaxime (p=0.014).(14)

*Insert Table 2 Here*

A comparison of the susceptibilities for isolates from the time-periods 2005-2010 and 2011-2014 is shown in Supplementary Table 2. This demonstrated statistically significant differences for several combinations, mostly reflecting an increase in susceptibility over time.

Carbapenem resistance was rare amongst the tested isolates with 97% demonstrating susceptibility. *Acinetobacter* sp.*, Pseudomonas* sp. and *Serratia* sp. exhibited the highest levels of resistance (40%, 5% and 3% respectively).

Extending the definition of EOS from 48h to 72h made no difference to the estimates of coverage for any combination tested, largely because so few isolates were obtained on day three (Supplementary Table 3).

Antimicrobial susceptibilities of specific pathogens

Both BNFC-recommended EOS combinations had complete coverage of the most commonly isolated pathogen Group B Streptococcus (GBS). There was no significant difference in the coverage of the 2nd most prevalent EOS pathogen, *E.coli,* between penicillin and gentamicin (94%) and amoxicillin and cefotaxime (90%) (p=0.53). Enterococcal species had high susceptibility to an amoxicillin and cefotaxime combination (93%).

Amongst common LOS pathogens, *E.coli* exhibited susceptibility in approximately 85% of cases to both BNFC-recommended combinations. *Enterococcus* sp. demonstrated high susceptibility rates to amoxicillin and cefotaxime (95%) while the contrary was true of *Enterobacter* sp. which were significantly more likely to be susceptible to flucloxacillin and gentamicin (59% vs. 82%, p<0.001). At least 88% of *Klebsiella* species were susceptible to each of these combinations (Table 3). The most prevalent individual organisms displaying resistance to common antimicrobial combinations are demonstrated in Supplementary Table 4.

*Insert Table 3 Here*

The *E.coli* associated with EOS were different to those associated with LOS. Of a total of 393 *E.coli* isolates reported, 258 (66%) had a complete antimicrobial susceptibility profile. Isolates causing LOS had significantly higher rates of antimicrobial resistance to a number of agents including amoxicillin and clavulanic acid (29% vs. 16% for EOS), cefotaxime (16% vs. 6%), ciprofloxacin (22% vs. 3%) and gentamicin (15% vs. 5%). High levels of resistance to amoxicillin/ampicillin (58-63%) were observed for both EOS and LOS isolates. LOS *E.coli* isolates were also 2.5 times more likely to demonstrate multi-drug resistance (i.e. to at least three tested classes of antimicrobial agents), than those causing EOS (p=0.039).

Antimicrobial susceptibilities by birthweight and gestation at birth

The two BNFC-recommended EOS combinations demonstrated high rates of coverage of EOS pathogens for infants >1500 grams and >32 weeks gestation (93-99%).(12) However, these combinations demonstrated significantly lower coverage rates in VLBW infants (<1500g) and the extremely preterm (<32 weeks) (79-92%, p=0.013 and 0.003 respectively). An amoxicillin and gentamicin combination demonstrated comparable levels of coverage to the benzylpenicillin and gentamicin combination for all birthweight and gestational age categories, with a non-significant trend towards improved coverage in infants <1500g and <32 weeks (93% vs. 86%) (p=0.211) (Supplementary Table 5).

For LOS, similar rates of coverage were seen across all birthweight and gestational age categories for each combination. For flucloxacillin and gentamicin, for example, the rates of coverage varied only from 86-92% (Supplementary Table 5).(14)

**Discussion**

EOS pathogens showed high rates of susceptibility to all four of the tested empiric antimicrobial combinations. The levels of susceptibility to the two BNFC (14) recommended combinations were approximately 95%; similar to those reported in previous UK studies.(17,18) Although high rates of susceptibility (95-98%) were reported for the cefotaxime-based regimens, due to the broadness of their spectrum of coverage and propensity to induce resistance there should be considerable reluctance to consider these as first-line empiric therapies for EOS.(16,19) The only exception to this would be the use of cefotaxime and amoxicillin in the setting of possible bacterial meningitis, due to the better CSF penetration associated with third generation cephalosporins.(20) It is also important to note that the absence of coverage of *Listeria* and enterococcal infections further reduces the effectiveness of cefotaxime monotherapy as a first-line choice for EOS.

Whilst a benzylpenicillin and gentamicin combination had satisfactory coverage of EOS pathogens in infants >32 weeks or >1500g, our results suggest that for infants of lower gestation and birthweight, the slightly broader spectrum combination of amoxicillin and gentamicin provides at least equivalent coverage, with a trend towards increased efficacy, in this population of neonates (93% vs. 86%, p=0.211). This raises the possibility that the above combination should be the preferred option for first-line therapy in these more premature infants. As the majority of babies receiving empiric antibiotics for EOS are born at term, it is however important to continue to use the more narrow spectrum combination (benzylpenicillin and gentamicin), in this group, especially given the coverage or pathogens is very high.

As would be expected, because LOS pathogens are generally nosocomially acquired, the LOS pathogens demonstrated higher levels of resistance than EOS pathogens. The very broad-spectrum combination of vancomycin and cefotaxime displayed coverage of over 91% of organisms tested. There should however be considerable reluctance in using this combination routinely given its high potential to develop antimicrobial resistance.(22) This policy is supported by the low mortality rate of coagulase negative staphylococcal (CoNS) infections (23) and the rarity of methicillin-resistant *Staphylococcus aureus* (MRSA) in our network.(22)

In total 89% of isolates were susceptible to flucloxacillin and gentamicin whilst 85% were susceptible to amoxicillin and cefotaxime.(17,18) In fact, these values are not statistically significantly lower than for vancomycin and cefotaxime. LOS pathogens were similarly susceptible to flucloxacillin and gentamicin across all birthweight and gestational age categories, supporting the continued routine use of this narrow-spectrum combination as a first line empiric therapy.(14)

*E.coli* isolates associated with EOS had different antimicrobial resistance patterns to those causing LOS. LOS *E.coli* were more frequently associated with higher levels of antimicrobial resistance to a variety of common antibiotics including amoxicillin and clavulanic acid, cefotaxime and gentamicin. This suggests that the *E.coli* isolates associated with vertical transmission are different to those which are associated with horizontal transmitted and supports the notion that they require treatment with different antimicrobial regimens.(18)

For all infants, regardless of age at onset or gestation at birth, none of the antibiotic combinations tested provide complete coverage against all pathogens. This raises the question of what comparative levels of coverage are acceptable, an issue which should also take into account the individual pathogens that are missed and their intrinsic virulence. It also means that clinicians should be vigilant in their regular assessment of the clinical effectiveness of the antimicrobial combination chosen in an individual neonate. Infants that are deteriorating despite ‘appropriate’ empiric therapy should be reviewed and antibiotics changed rather than waiting for blood culture results. This concept is included in the NICE guidelines.(15)

The primary strength of the neonIN database is its size and longitudinal design, incorporating 30 neonatal units over 10 years, however a number of potential limitations must also be acknowledged. Firstly, the infection definition may be considered too simplistic or subjective given its reliance on the clinician’s judgement. This subjectivity may lead to over-reporting of cases, particularly of common skin contaminants. An alternative would be to incorporate more clinical and laboratory markers into the study definition, but this may then in turn affect the completeness and quality of data entered.

It is also important to acknowledge the fact that some antimicrobial combinations act synergistically (e.g. benzylpenicillin and gentamicin), and that resistance to the constituent antimicrobial agents in a combination may not equate to resistance to the combination itself.(24) Conversely, it must be acknowledged that in some cases the reported in-vitro susceptibility to an antimicrobial agent does not mean that it is recommended for the treatment of that organism (e.g. cephalosporins for enterobacter). Both these factors are difficult to account for and may affect the generalisability of the stated results.

The statistical analyses used may also provide a potential source of bias as we have converted raw susceptibility data into a more clinically relevant format which is combination based. This may create issues in cases where testing is done for only one antibiotic, as the combination is therefore labeled as susceptible or resistant accordingly. For example, the difference between cefotaxime monotherapy and an amoxicillin and cefotaxime combination may be explained by isolates with a recorded susceptibility profile to amoxicillin alone (e.g. resistant). As such the isolate would be labeled as resistant to the combination but ‘not tested’ for cefotaxime monotherapy.

Data completeness is always a potential weakness. However, although only half of the pathogens had susceptibility data recorded we have no evidence to suggest that these isolates were not representative. We also believe that the conclusions are relevant for all UK tertiary neonatal units as this reflects the case-mix found in the neonIN network, with units spread widely throughout England. We do however note the presence of dominant reporting centres, with 10 units providing data on >50 isolates. This may impact the generalisability of the data.

These results highlight a number of important areas for future research, particularly with respect to the use of risk-factor based guidelines for empiric antimicrobial policies. The introduction of such guidelines, for example those proposed for infants <1500g or <32 weeks gestation, would be of significant clinical value if further validated. Future research in this area would inform the development of a simple and clinically relevant guideline which could easily be implemented in neonatal units.

This study provides unique insights into the antimicrobial resistance patterns exhibited by the pathogens which commonly cause neonatal infections in tertiary UK neonatal units. It presents new data of clinical value which could provide direction for the development of novel risk-factor based guidelines for empiric antimicrobial treatment which may in turn lead to better health outcomes for our neonatal population.

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|  |  |  |
| --- | --- | --- |
|  | **Antibiotic 1** | **Antibiotic 2** |
| **Early Onset Sepsis** | Benzylpenicillin | Gentamicin |
| Amoxicillin | Cefotaxime |
| Amoxicillin | Gentamicin |
| Cefotaxime |
| **Late Onset Sepsis** | Flucloxacillin | Gentamicin |
| Amoxicillin | Cefotaxime |
| Amoxicillin | Gentamicin |
| Piperacillin/Tazobactam | Gentamicin |
| Vancomycin | Cefotaxime |
| Cefotaxime |
| Amoxicillin & Clavulanic acid |

**Table 1: Commonly used empiric antibiotic combinations in the treatment of neonatal sepsis.** Adapted from the British National Formulary for Children recommendations, Muller-Pebody et al. and Vergnano et al.(10,12,15)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Combination | # Tested | # Susceptible | % Susceptible (95% CI) |
| EOS | Benzylpenicillin | Gentamicin | 238 | 222 | 93 (89-96) |
| Amoxicillin | Cefotaxime\* | 228 | 216 | 95 (91-97) |
| Amoxicillin | Gentamicin | 238 | 229 | 96 (93-98) |
| Cefotaxime\* | 193 | 189 | 98 (95-99) |
| LOS | Flucloxacillin | Gentamicin | 833 | 742 | 89 (87-91) |
| Amoxicillin | Cefotaxime | 783 | 665 | 85 (82-87) |
| Amoxicillin | Gentamicin | 876 | 770 | 88 (86-90) |
| Piperacillin/Tazobactam | Gentamicin | 317 | 279 | 88 (84-91) |
| Vancomycin | Cefotaxime | 763 | 700 | 92 (90-94) |
| Cefotaxime | 538 | 475 | 88 (85-91) |
| Amoxicillin & Clavulanic acid | 657 | 526 | 80 (77-83) |

**Table 2: Susceptibility of pathogens to commonly used antimicrobial combinations.** Susceptibility levels (%) of early onset and late onset pathogens in the neonIN cohort to commonly used antibiotic combinations for the treatment of neonatal sepsis. Cefotaxime monotherapy demonstrated the highest rate of susceptibility for early onset pathogens (98%), whilst the two most commonly used empiric combinations, benzylpenicillin and gentamicin or amoxicillin and cefotaxime, demonstrated rates of 93% and 95% respectively. A combination of vancomycin and cefotaxime displayed the highest rates of microbial susceptibility among late onset pathogens (91%) with the commonly prescribed combination of flucloxacillin and gentamicin demonstrating the second highest rate of coverage (89%). # = Number of isolates, % = Percentage of isolates, EOS = Early onset sepsis, LOS = Late onset sepsis. 95% CI = 95% confidence interval.
\*Please note that while it may seem counter-intuitive that these figures should differ, this is due to the fact that isolates where testing is done for one antibiotic in a combination but not the other are marked as susceptible or resistant according to that agent. Therefore the difference between cefotaxime monotherapy and an amoxicillin and cefotaxime combination is due to isolates labelled as resistant to amoxicillin and for which cefotaxime is untested. As such the isolate is labeled as resistant to the amoxicillin and cefotaxime combination but ‘not tested’ for cefotaxime monotherapy.

(a)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen | % of all EOS isolates | Benzylpenicillin & Gentamicin | Amoxicillin & Cefotaxime |
| # Tested | % Susceptible | # Tested | % Susceptible |
| Group B Streptococcus | 44% | 106 | 99 | 110 | 99 |
| *E.coli* | 19% | 65 | 94 | 63 | 90 |
| *Streptococcus* sp. | 11% | 28 | 100 | 21 | 95 |
| *Micrococcus* sp. | 4% | 4 | 100 | 0 | N/A |
| *Enterococcus* sp. | 4% | 3 | 33 | 14 | 93 |

(b)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen | % of all LOS isolates | Flucloxacillin & Gentamicin | Amoxicillin & Cefotaxime |
| # Tested | % Susceptible | # Tested | % Susceptible |
| *Enterococcus* sp. | 17% | 22 | 0 | 177 | 95 |
| *E.coli* | 16% | 186 | 84 | 180 | 86 |
| *S.aureus* | 16% | 160 | 98 | 2 | 50 |
| *Klebsiella* sp. | 11% | 134 | 92 | 137 | 88 |
| *Enterobacter* sp. | 9% | 106 | 82 | 99 | 59 |

**Table 3: Susceptibility of the 5 most common pathogens causing neonatal sepsis to BNFC-recommended antimicrobial combinations for a) early-onset sepsis and b) late-onset sepsis.** Number of isolates tested and susceptibility rate for the most prevalent pathogens of both (a) early-onset and (b) late-onset sepsis. Almost all the most common pathogens of early onset sepsis demonstrated high levels (>=90%) of susceptibility to both first-line antimicrobial combinations. Approximately 15% of E.coli isolates displayed resistance to both late-onset sepsis combinations. # = Number of isolates, % = Percentage of isolates.

**Associated ‘Boxes’ of Background Information**

**What is already known on this topic:**

* Neonates with presumed sepsis require empiric antibiotic treatment before definitive culture results are available. A thorough understanding of epidemiology and resistance patterns is therefore imperative.
* The development and spread of antimicrobial resistance is an important issue in modern medicine.
* There is a paucity of new antibiotics to replace the current agents should they be rendered obsolete reinforcing the importance of choosing empiric combinations wisely.

**What this study adds:**

* A benzylpenicillin and gentamicin combination has very high coverage of EOS pathogens in infants >32 weeks or >1500g.
* For infants of lower gestation and birthweight, the combination of amoxicillin and gentamicin may provide better coverage.
* Clinicians should be vigilant in their assessment of the clinical effectiveness of the antimicrobial combination chosen in an individual neonate.