**NEONATAL GRAM NEGATIVE INFECTIONS, ANTIBIOTIC SUSCEPTIBILITY AND clinical OUTCOME: An observational study**

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**Background**

Neonatal Gram negative (GN) infections are associated with high mortality and morbidity. Early appropriate antibiotic treatment is vital and gentamicin is the most frequently used antibiotic on neonatal units (NNU). Antimicrobial breakpoints are predominantly based on adult data and the relationship between minimum inhibitory concentrations (MIC) and outcome in neonates is unclear.

We aimed to determine the MIC of GN pathogens causing neonatal infections and relate this to clinical outcomes.

**Methods**

MICs for 8 antibiotics plus extended spectrum beta-lactamase production were determined for invasive GN bacterial isolates from 8 UK NNUs. EUCAST breakpoints were applied. MIC was correlated with clinical outcome using multivariable regression analysis.

**Results**

118 episodes from 116 patients were analysed. The median birth gestation and median postnatal age was 27 weeks (IQR 24.6-32.3) and 20 days (IQR 5-44) respectively. Pathogens included *E.coli* (51%), *Klebsiella* spp. (23%) and *Enterobacter* spp*.* (22%). 10 day attributable mortality was 18.1% (21 patients) with the highest mortality from *P. aeruginosa* infections (43%). ESBL producers accounted for 13.8% of the isolates.

In regression analysis, increasing gentamicin MIC was associated with increased mortality in gentamicin treated patients across the full MIC range (OR per loge increase in MIC: 2.29; 95% CI 1.23-4.26, p=0.009), including susceptible isolates only (MIC≤4) (OR: 3.05; 95% CI 1.10-8.46, p=0.032).

**Conclusion**

Neonatal mortality from GN infections remains high and is associated with increasing gentamicin MIC, even for isolates deemed susceptible. A better understanding of population-specific MICs and aminoglycoside dosing is required to guide empiric antibiotic treatment.

**Introduction**

Infection is a leading cause of morbidity and mortality in neonates and, despite on-going improvements in neonatal care, infection rates remain static. [1,2] Gram negative (GN) organisms are responsible for a significant proportion of infections and premature infants are particularly at risk as a result of innate and adaptive immune system immaturity in addition to the invasive intensive care required for survival. [3–5]

The National Institute for Health and Care Excellence recommends gentamicin (combined with a penicillin) for the treatment of suspected early onset infection and gentamicin is the most commonly prescribed drug on neonatal units (NNUs). [6,7] In this empiric combination for early onset infection gentamicin is the antibiotic agent targeting Gram negative pathogens. A wide range of other antibiotics are used for hospital acquired infections in UK NNUs, depending on local antibiotic sensitivities and unit preferences.[8]

Antimicrobial susceptibility thresholds (breakpoints) are derived by the European Committee on Anti-microbial Susceptibility Testing (EUCAST) based on typical drug doses and formulations, epidemiological cut-off values (determined from minimum inhibitory concentration (MIC) distribution data), pharmacokinetic-pharmacodynamic (PK/PD) data and clinical outcomes, predominantly in adult patients. [9] However, break points for special populations, including neonates, have not been developed.

Whilst high rates of antibiotic resistance have been reported in neonatal units in many countries, few data are available concerning the resistance profiles of infections occurring in UK neonatal units. [10,11] Multidrug resistance is associated with a higher mortality in neonates[12] and an association between increased MIC within the susceptible range and mortality from GN infections has also been shown in adults. [13] This has not yet been reported in neonates.

We aimed to characterise invasive Gram negative infections within a neonatal infection surveillance network in the United Kingdom, determine their antibiotic susceptibility and assess the impact of antibiotic susceptibility on clinical outcomes.

**Methods**

**Participants**

Units participating in the neonIN infection surveillance network (www.neonin.org.uk) were approached to contribute to this study. Infants with Gram negative bacteraemia (defined as the presence of any Gram negative isolate in one or more blood cultures) were identified from 8 NNUs (6 neonatal intensive care units, 2 local neonatal units) over a 4.5 year period (November 2009 - July 2014). Anonymised clinical data including birth gestation, birth weight and age at infection, antimicrobials administered for that infection episode, relapses (defined as growth of the same organism within 28 days of a sterile culture following infection), length of stay and attributable and non-attributable mortality were collected using a standardised case report form. The date of the first negative culture was obtained if performed. Early onset sepsis (EOS) was defined as occurring within the first 2 days of life. Death was assessed as infection-related by the patient’s attending clinician.

NeonIN is a registered research database and has received approval from the National Research Ethics Service Committee London - Surrey Borders (REC reference 05/Q0806/34+5). Individual consent is not required as only anonymised data, on infection episodes, are recorded and stored on the neonIN database.

**Microbiological analysis**

Bacterial isolates are routinely stored as a part of clinical practice. The isolates are retained for a variable amount of time by each laboratory, so not all centres had isolates available for the whole study period. Stored GN isolates were sent to the Department of Microbiology at St George’s, University of London. A pure growth of bacteria was obtained and identified by Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF, Brucker Germany) mass spectrometry. The MIC was determined for the following antibiotics: amikacin, cefotaxime, ciprofloxacin, co-amoxiclav, colistin, gentamicin, meropenem and piperacillin-tazobactam. The MIC was determined using Etest (BioMerieux, Marcy l’Etiole, France) or MIC-E (Oxoid, Hampshire, UK) in accordance with manufacturer’s instructions. Extended spectrum beta-lactamase (ESBL) production was determined by a combination of ESBL E-Tests (cefotaxime / cefotaxime + clavulanic acid, ceftazidime / ceftazidime + clavulanic acid and cefepime / cefepime + clavulanic acid). Infrequent pathogens (<5 isolates of the same genus) were not analysed.

**Statistical analysis**

Each infant was included for their first episode of GN infection only. The data were not all normally distributed and therefore nonparametric tests of statistical significance were used as appropriate (Kruskal-Wallis one-way analysis of variance or Mann-Whitney U test). A value of p<0.05 was defined as statistically significant.

To quantify associations between MIC and 10 day attributable mortality and relapse, multivariable backwards stepwise logistic regression was performed using loge transformed MIC values for each antibiotic in the patients who had received one or more antibiotic doses. Other variables entered in the model included gestation, postnatal age at infection onset and pathogen. This was performed separately for the whole distribution of MICs and those within the susceptible range only. A 10 day cut-off for attributable mortality was used as early mortality was assumed to be more likely a direct consequence of infection than late mortality. Amikacin and cefotaxime were not included in regression analysis as too few patients received them.

All data were analysed using STATA version 13 (Stata Inc, College Station, Tx).

**Results**

**Patients**

A total of 148 isolates were received from 149 infection episodes and 129 isolates had MIC analysis performed. Matching clinical information was available for 116 patients (56.7% male) who had infections with 118 isolates (figure 1). The median gestation at birth was 27.0 weeks (IQR 24.6-32.3 weeks) and the median birth weight was 865g (IQR 635-1620g). There was no difference in gestation or birth weight by pathogen (p=0.37 and p=0.89 respectively).

The median postnatal age at bacteraemia was 20 days (IQR 5-44) with significant differences between pathogens (table 1, p<0.001). EOS represented 13.8% of all GN infections (16/116).

The median maximum CRP was 82 mg/L (IQR 16-141; no significant difference between pathogens, p=0.54); 15 (12.9%) patients had concurrent necrotising enterocolitis, 2 patients had meningitis (1.7%) and 2 patients a concurrent urinary tract infection (1.7%).

**Pathogens**

The most frequent pathogens were *E. coli* (59), *Enterobacter* spp. (27), *Klebsiella* spp. (26), *Pseudomonas aeruginosa* (8) and *Serratia marcescens* (8) (figure 1). The MIC distributions for these pathogens are shown in figure 2, figure 3; supplementary tables 1-8. ESBL production varied by pathogen (p<0001): *E. coli* (4/59, 6.8%), *Enterobacter* spp. (7/27, 25.9%), *Klebsiella* spp. (4/27, 14.8%), *P. aeruginosa* (6/8, 75%) and *S. marcescens* (1/8, 12.5%). There were 2 indeterminate results (1 *P. aeruginosa*, 1 *E. cloacae*).

**Clinical Outcomes**

Clinical outcomes are shown in table 1. Overall attributable mortality was significantly lower in infants with Klebsiella infections (OR 0.22, 95% CI 0.06-0.83; p=0.026) compared with other infections; 15 of the 22 Klebsiella infections occurred in infants from one hospital. There was only one relapse, a *Klebsiella oxytoca* infection occurring 14 days after a sterile blood culture in a term infant with a concomitant urinary tract infection.

There were no statistically significant differences between pathogens in the following clinical outcomes: time to death (p=0.25), time to negative culture (p=0.060), duration of antibiotic therapy (p=0.67), duration of hospital stay following the infection episode (p=0.94) and discharge destination (i.e. to home or another hospital) (p=0.56). The median number of antibiotics per patient was 3 (IQR 2-4) and there was considerable variation in the antibiotic regimens administered (Supplementary table 9).

**Relationship between MIC and outcome**

Gentamicin was the most frequently used antibiotic (76/116, 65.5% patients) with a median duration of 5 days (IQR 2-8). In addition to gentamicin, 68/76 (89.5%) of patients received other antibiotics with activity against Gram negative bacteria and 59/76 (77.6%) received a β-lactam antibiotic. The isolates obtained from these 76 patients included 40 *E. coli* (53%), 14 *Klebsiella* spp. (18%), 13 *Enterobacter* spp. (17%), 4 *Pseudomonas aeruginosa* (5%) and 5 *Serratia* spp (7%). Resistance according to EUCAST criteria was found in 3 isolates (all *E. coli*) and 28 patients died (36.8%). The mortality in those with gentamicin resistant strains was 100% (3/3) compared with 34% (25/73) in those with susceptible strains (p=0.047). In the regression analysis (table 2), a significant increase in mortality for each loge increase in gentamicin MIC was seen (OR 2.29; 95% CI 1.23-4.26) which remained when resistant isolates were excluded from the analysis (OR 3.05; 95% CI 1.10-8.46). No association was found between MIC and outcomes for any other individual antibiotics. An association between ESBL production and increased MICs to other antibiotics was found (Supplementary table 10). However there was no significant difference in 10-day attributable mortality (p=0.73), hospital length of stay (p=0.87) and antibiotic duration (p=0.29) in patients infected with ESBL-producing organisms compared with non ESBL-producing organisms.

The number of relapse episodes was not sufficient to allow analysis according to MIC.

**Discussion**

This study provides current and detailed antibiotic susceptibility and outcome data for invasive Gram negative infections within a large multi-centre cohort and, to our knowledge, is the first study to demonstrate that increasing gentamicin MIC, even within the predefined ‘susceptible’ range, may be associated with increased mortality in gentamicin treated infants.

Consistent with previous studies, the majority of GN infections occurred in extremely premature and low birth weight infants and, with the exception of *E. coli*, were late onset (hospital acquired) infections, reflecting the on-going intensive care these infants require. [3,14,15]

The relative frequency of different pathogens in this study closely resembles those previously reported; Gordon *et al.* reported an almost identical GN pathogen distribution in an Australian study of 16 NNUs conducted between 1992-2002. Disappointingly, but perhaps unsurprisingly given the increasing numbers of extremely preterm infants surviving beyond the first week of life, the mortality associated with GN infection also appears to be unchanged over the last 2 decades. Gordon *et al.* reported 20.8% attributable mortality compared with 19.8% in our cohort and 18.0% was reported in an American study including 6215 preterm infants conducted between 1998-2000 (reduced from 28% in 1988-1997). [16,17]

Relatively little surveillance data on antibiotic susceptibility is available for the neonatal and infant population. The Antibiotic Resistance and Prescribing in European Children (ARPEC) project which included 392 GN infections in children under 1 year of age from 12 European countries, reported higher rates of aminoglycoside and 3rd generation cephalosporin resistance for *Klebsiella* spp. and similar rates of gentamicin, 3rd generation cephalosporin, ciprofloxacin and carbapenem resistance for *E. coli* infections [18] compared with our cohort. Lutsar *et al*. also reported significantly higher rates of resistance for enterobacteriaceae (ranging from 10% for meropenem to 40% for piperacillin-tazobactam) in a smaller cohort of 24 infants from neonatal units across 5 European countries and a 17% infection-related mortality. [19] However, the UK national antibiotic susceptibility surveillance data (which reports all age groups together) detailed similar rates of gentamicin, 3rd generation cephalosporin, ciprofloxacin and carbapenem susceptibility for *E. coli* and *Klebsiella pneumoniae* infections as our neonatal cohort. [20]

This study suggests that among babies with GN bacteraemia there may be a significant increase in mortality associated with bacteria with higher gentamicin MICs. A previous study reported 376 GN infections over a 7 year period in a Taiwanese NICU and demonstrated an increased mortality if multi-drug resistance was present (OR 1.67) but did not report single antibiotic MICs. [21]

Given that gentamicin is widely recommended for empirical treatment of both early and late onset sepsis, this finding is of concern. One possibility to explain this is that these infants simply did not achieve sufficient peak gentamicin blood concentrations. Guidelines recommend that gentamicin concentrations of ≥8mg/L should be aimed for in the presence of Gram negative bacteraemia, around 3-5 times MIC [6,22]. However, peak concentrations are rarely measured in routine neonatal practice, which is focused around gentamicin trough levels and prevention of oto- and nephrotoxicity, and we do not know what peak concentrations were achieved in babies in this study. However, all NNUs in the study used the recommended gentamicin dosing regimen of 4-5mg/kg/dose[23], which has been shown to achieve sufficient peak concentrations. [24]

Another possibility is that the current EUCAST gentamicin susceptibility breakpoint (2mg/L) is too low for GN infections in this special population and a new breakpoint may be needed. This is plausible, because successful killing of a pathogen is brought about not only by sufficient antibiotic concentrations but also by the host’s immunological response, which is likely to be naïve in newborns. There is a need for further work to improve our understanding of gentamicin PK/PD and susceptibility breakpoints in neonates.

A further potential explanation concerns the possibility of co-resistance. We have shown, for example, that the ESBL producing organisms in this study were also more likely to have higher MICs against other antibiotics tested (including gentamicin). This can be explained by the presence of plasmids that encode mutations to multiple antibiotics.[25] However, as indicated there was no association found between the MIC and outcomes for any other specific antibiotics and nor was there any association found between ESBL organisms and outcomes.

Several previous adult studies have reported conflicting findings on the relationship between MIC and outcome with Gram positive infections. [26–28] Findings from studies of GN infections suggest improved outcome with lower MICs for carbapenems, fluroquinolones and piperacillin-tazobactam, and a meta-analysis of GN infections in predominately adult patients found that higher fluoroquinolone MIC values were associated with an increased risk of treatment failure in Salmonella infections, and increased mortality and treatment failure in non-fermentative GN infections [13,29,30].

**Strengths and limitations**

Our study included a large number of GN pathogens isolated from babies on NNUs across England and determined the MIC for a number of routinely used antibiotics, however it does have some limitations.

This was a retrospective observational study and as such there is the possibility of missing data and confounders of association. In particular, nearly all patients received multiple antibiotics and the reasons for changing antibiotic therapy were not always well documented, making treatment failure difficult to assess. Due to the high number of different antibiotic combinations and frequent changes it was not possible to look at the effect of empirical antibiotic combinations on outcome, instead we focused on the most frequently administered antibiotics.

Despite including a number of tertiary NNUs over a period of 5 years the number of infections due to each individual pathogen was relatively small limiting our ability to relate outcomes to specific pathogens. To address this we included all pathogens in the regression analysis but there may have been between pathogen differences which we were unable to detect due to the small sample size.

In summary, neonatal GN resistance profiles are similar to those reported in adults in the UK and generally demonstrate high rates of susceptibility to commonly used antibiotics. Despite this the GN mortality remains unchanged over 2 decades and a higher gentamicin MIC, even within the ‘susceptible’ range, may contribute to this. Prompt addition of a further antimicrobial agent with activity against Gram negative bacteria and targeting high gentamicin peak concentrations, in accordance with NICE guidelines, may help to reduce this mortality [6] but further work is required to understand and therefore optimise antimicrobial, and in particular aminoglycoside, therapy in neonates.

**Conclusion**

This study provides detailed MIC data on GN pathogens in UK NNUs and demonstrates an association between increasing gentamicin MIC and mortality in patients receiving gentamicin to treat Gram negative infections. Further PK/PD studies are required to optimise aminoglycoside dosing in neonates to improve clinical outcomes.

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**Author contribution statement;**

All authors contributed to the design of the study and reviewed the draft manuscript. In addition AK, CK, IMM, TDP conducted the microbiological and statistical analysis.

**Conflicts of interest:**

PTH was a member of the National Institute of Health and Clinical Excellence Antibiotics for Early Onset Neonatal Infection Guideline Development Group.

What is known on this topic:

* Gram negative infections in neonates affect the smallest and most premature infants and are often late onset, hospital acquired infections.
* Resistance against multiple antibiotics is associated with poor clinical outcome
* Antimicrobial susceptibility recommendations are mainly derived from adult data

What this study adds:

* Mortality due to Gram negative infections remains unchanged over the last 2 decades
* Detailed information on antibiotic susceptibility for invasive Gram negative infections on UK neonatal units is now available
* Increasing gentamicin minimum inhibitory concentration, even in the ‘susceptible’ range may be associated with increased mortality.

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Table 1: Outcome data, overall and by pathogen. Median (IQR), n (%). \*excludes those who died

Table 2: Multivariable regression analysis for 10-day attributable mortality by antibiotic. For ciprofloxacin, piperacillin-tazobactam and co-amoxiclav no variables were retained in the stepwise backwards model (p>0.2 for all). PNA: Postnatal age.

Table 1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Overall** | ***E. coli***  **(n=57)** | ***Klebsiella* spp. (n=23)** | ***Enterobacter* spp. (n=22)** | ***P. aeruginosa* (n=7)** | ***S. marcescens***  **(n=7)** |
| Gestation (weeks) | 27.0  (24.6-32.6) | 26.6  (24.1-32.6) | 27.4  (26.3-37.6) | 26.5  (24.0-30.7) | 24.6  (24.3-27.1) | 29.0  (26.7-33.6) |
| Birth weight (g) | 860 (635-1640) | 860 (660-1735) | 990 (677-2273) | 748 (608-1430) | 630 (620-985) | 1080 (600-1460) |
| Postnatal age (days) | 20 (5-44) | 7 (1-29) | 33 (15-91) | 44 (26-68) | 19 (5-29) | 18 (10-27) |
| Died (all cause) | 36 (31.0) | 23 (40.4) | 3 (13.0) | 7 (31.8) | 4 (57.1) | 0 |
| Died (attributable to the infection) | 23 (19.8) | 17 (29.8) | 1 (4.3) | 2 (9.1) | 3 (42.8) | 0 |
| 10 day mortality (attributable) | 21 (18.1) | 16 (28.0) | 1 (4.3) | 1 (4.5) | 3 (42.8) | 0 |
| Time to death (attributable) (days) | 3 (0-6) | 1 (0-4) | 3 | 17 (8-26) | 1 (0-9) | NA |
| Negative culture obtained | 66 (56.9) | 29 (50.8) | 16 (76.2) | 16 (72.7) | 2 (33.3) | 3 (42.9) |
| Time to negative culture (days) | 5 (3-10) | 6 (4-23) | 4 (2-6) | 4 (3-6) | 2 (2-2) | 5 (2-6) |
| Duration of antibiotics (days)\* | 12 (8-16) | 12 (8-15) | 12 (10-19) | 14 (8-17) | 14 (8-24) | 10 (7-14) |
| Discharged home | 28 (24.1) | 13 (22.8) | 9 (39.1) | 4 (18.2) | 0 | 2 (28.6) |
| Transferred to another unit | 50 (43.1) | 21 (36.8) | 11 (47.8) | 10 (45.5) | 3 (42.9) | 5 (71.4) |
| Time to discharge (days)\* | 51 (19-70) | 57 (10-80) | 47 (20-66) | 57 (23-86) | 39 (8-62) | 33 (21-56) |

Table 2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **All isolates** | | | **Susceptible isolates only** | | |
| **OR (95% CI)** | **Standard error** | **p** | **OR (95% CI)** | **Standard error** | **p** |
| **Gentamicin** | | | | | | |
| MIC (loge) | 2.29 (1.23-4.26) | 0.73 | 0.009 | 3.05 (1.10-8.46) | 1.59 | 0.032 |
| PNA (days) | 0.96 (0.92-1.00) | 0.02 | 0.058 | 0.95 (0.90-1.00) | 0.02 | 0.039 |
| Gestation (weeks) | 0.81 (0.68-0.96) | 0.07 | 0.014 | 0.83 (0.71-0.97) | 0.07 | 0.020 |
| **Meropenem** | | | | | | |
| Gestation (weeks) | 0.83 (0.63-1.09) | 0.12 | 0.19 | 0.83 (0.63-1.09) | 0.12 | 0.19 |