High carriage rates of multidrug-resistant Gram-negative bacteria in neonatal intensive care units from Ghana

Labi, Appiah-Korang; Bjerrum, Stephanie; Enweronu-Laryea, Christabel C; Ayibor, Prosper K; Nielsen, Karen L; Marvig, Rasmus L; Newman, Mercy J; Andersen, Leif P; Kurtzhals, Jorgen A L

Published in: Open Forum Infectious Diseases

DOI: 10.1093/ofid/ofaa109

Publication date: 2020

Document version: Publisher's PDF, also known as Version of record

Document license: CC BY

High Carriage Rates of Multidrug-Resistant Gram-Negative Bacteria in Neonatal Intensive Care Units From Ghana

Appiah-Korang Labi,1,2,6 Stephanie Bjerrum,4 Christabel C. Enweronu-Laryea,5 Prosper K. Ayibor,6 Karen L. Nielsen,7 Rasmus L. Marvig,7 Mercy J. Newman,6 Leif P. Andersen,3 and Jorgen A. L. Kurtzhals2,3

1Department of Microbiology, Korle-Bu Teaching Hospital, Accra, Ghana, 2Centre for Medical Parasitology at Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark, 3Department of Clinical Microbiology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, 4Department of Public Health, Global Health Section, University of Copenhagen, Copenhagen, Denmark, 5Department of Child Health, University of Ghana Medical School, Accra, Ghana, 6Department of Medical Microbiology, University of Ghana Medical School, Accra, Ghana, 7Centre for Genomic Medicine, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, 8Department of Medical Microbiology, University of Ghana Medical School, Accra, Ghana

DOI: 10.1093/ofid/ofaa109

Open Forum Infectious Diseases

© The Author(s) 2020. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Background. Carriage of multidrug resistant (MDR) Gram-negative bacteria (GN) in hospitalized neonates may increase the risk of difficult-to-treat invasive infections at neonatal intensive care units (NICUs). Data on MDRGN carriage among hospitalized newborns in Africa are limited.

Methods. We conducted a cross-sectional study at the NICUs of 2 tertiary hospitals in Ghana. Swabs from the axilla, groin, perianal region, and the environment were cultured, GN were identified, and antibiotic susceptibility was tested. We obtained blood culture isolates from neonates with sepsis. Whole-genome sequencing was used to characterize carbapenemase-producing Klebsiella pneumoniae. Typing was done by multilocus sequence typing (MLST) and single nucleotide polymorphism (SNP) analysis.

Results. A total of 276 GN were isolated from 228 screened neonates. Pathogenic GN were cultured in 76.8% (175 of 228) of neonates. Klebsiella spp (41.7%; 115 of 276) and Escherichia coli (26.4%; 73 of 276) were the commonest organisms. Carriage rates of MDRGN and third-generation cephalosporin resistant organisms were 49.6% (113 of 228) and 46.1% (105 of 228), respectively. Among Klebsiella spp, 75.6% (87 of 115) phenotypically expressed extended-spectrum β-lactamase activity, whereas 15.6% expressed carbapenemase and harbored blaTEM-1,blaOXA-181, and blaCTX-M-15. Overall, 7.0% (16 of 228) of neonates developed GN bloodstream infection. In 2 of 11 neonates, sequencing showed the same identity between carriage and the bloodstream isolate. Length of stay before specimen collection and antibiotic use were independently associated with carriage rates, which increased from 13% at admission to 42% by day 2 and reached a plateau at 91% by day 15.

Conclusions. High carriage rates of MDRGN, including carbapenemase-producing enterobacterales may be an emerging problem in NICUs in Africa.

Keywords. carbapenemase; carriage; Ghana; multidrug resistant; neonates.

There is an increase in the global burden of infections with multidrug-resistant Gram-negative bacteria (MDRGN) in neonates, particularly in low-resource settings [1, 2]. Carriage of MDRGN, especially Klebsiella pneumoniae and Escherichia coli, is associated with late-onset neonatal bloodstream infections (BSIs) [3]. MDRGN can be transmitted from colonized individuals to other patients and persist in the environment due to poor infection prevention and control practices [4, 5]. MDRGN such as extended-spectrum β-lactamase (ESBL) and carbapenemase-producing enterobacterales have been associated with difficult-to-treat infections, increased length of hospitalization, and increased risk of mortality [5, 6].

Screening critically ill patients for carriage of MDRGN helps in controlling the spread of antibiotic-resistant organisms [7] by allowing timely implementation of preventive measures [4, 8]. However, its usefulness in areas with endemic or rare occurrence of MDR organisms as well as its role in predicting sepsis remains controversial [9, 10].

In recent years, maternal-newborn interventions in low- and middle-income countries (LMICs) such as Ghana have led to more women giving birth in health facilities [11]. However, the infrastructural and human resources needed to provide effective hospital-based services are often deficient leading to overcrowding of neonatal intensive care units (NICUs) and increased risk for healthcare-associated infections [12, 13]. Few studies have examined the carriage of MDRGN in NICUs in sub-Saharan Africa. Local data are critical for developing evidence-based treatment guidelines and protocols for infection...
prevention and control. In this cross-sectional study, we conducted risk factor analysis for carriage of MDRGN and used whole-genome sequencing (WGS) to understand resistance mechanisms and sources of transmission in NICUs at 2 tertiary hospitals in Ghana.

MATERIALS AND METHODS

Study Design and Population

During the baseline period of an ongoing study evaluating infection control interventions against neonatal sepsis and MDRGN carriage (clinicaltrials.gov NCT03755635) [14], we conducted a cross-sectional study at the NICUs of 2 tertiary hospitals in Accra, Ghana. Data collection took place in September 2017 and January 2018. This timeline was chosen to ensure that neonates sampled the first time would have been discharged by the second sampling, thus reducing the chance of repeat sampling. Swabs were collected from all neonates on admission at the NICUs on a single day in September 2017 and in January 2018. To increase the proportion of newly admitted neonates in our dataset and thereby assess MDRGN carriage before admission, we collected swabs during the admission processes for a period of 14 days after the initial specimen collection.

Study Sites

The NICU at Korle-Bu Teaching hospital (KBTH) is a 55-bed facility, with 3 cubicles for high-dependency care and a 5-bed kangaroo mother care ward. It admits approximately 2400 neonates a year [15]. The 37 Military Hospital (37MH) NICU has 20 beds, it is divided into 3 cubicles, and it admits approximately 800 neonates annually. The first-line empiric antibiotic used for neonatal sepsis at the KBTH was clavulanic acid and amikacin, whereas empiric antibiotics used for sepsis treatment at the 37MH varied. Routine screening for MDRGN carriage was not standard practice at the 2 hospitals. Neonates were generally admitted on the day of birth usually without prior antibiotic administration. Thus, the microbiota of freshly admitted newborns is likely to reflect maternal microbiota.

Clinical Data

Clinical data extracted from patient records on the day of specimen collection included maternal pregnancy history, birth weight, reason for admission, and antibiotic use before specimen collection. Data on maternal receipt of antibiotics and group B Streptococcus carriage were not recorded, and we did not screen mothers for carriage of MDRGN.

Specimen Collection and Microbiology Analysis

Swabs were collected from neonates by a trained nurse using BBL culture swab liquid Amies Medium (Becton Dickinson, Franklin Lakes, NJ). Each sample was taken with a swab moistened in transport medium and gently rotated in the fossa of the pinna, axilla, groin, and perianal region (in that order). These sites were chosen because of documented increased chance of isolating MDRGN [16]. All swabs were initially cultured on MacConkey agar plates at 35–37°C. Different GN colony morphotypes were identified and stored at −80°C and transported on dry ice to the Department of Clinical Microbiology, Rigshospitalet (Copenhagen, Denmark). Frozen isolates were thawed and cultured on lactose agar plates (SSI Diagnostica, Hillerød, Denmark) to recover GN, which were identified using MALDI Biotyper (Bruker Daltonics, Bremen, Germany).

During the study period, we conducted 3 environmental screenings at the KBTH (September 2017, October 2017, and January 2018, respectively) to understand the role of the environment in the spread of MDRGN infections. Sites (incubator doors, cots, trolley handles, door handles, weighing scales, tables, and desks) were screened using Replicate Organism Detection and Count (RODAC) plates filled with tryptic soy agar for flat surfaces; for uneven surfaces, a swab was taken.

Antibiotic susceptibility testing was performed on Müller-Hinton medium (SSI Diagnostica) by the Kirby Bauer disc diffusion method. All zone diameters were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [17]. Zone sizes within the intermediate resistance and absolute resistant range were classified as resistant. All enterobacterales were assessed for ESBL, and isolates with a meropenem zone <28 mm were assessed for carbapenemase expression. These tests were performed and interpreted according to EUCAST guidelines [18], using ROSCO (Taasstrup, Denmark) phenotypic ESBL + AMPC and KPC + MBL + OXA-48 carbapenemase Kit. Multidrug resistance was defined as nonsusceptibility to ≥1 antibiotic in ≥3 antibiotic groups, with the following antibiotics used in the classification: gentamicin/amikacin, piperacillin tazobactam, meropenem, cefuroxime, cefotaxime, ciprofloxacin, and amoxicillin-clavulanic acid [19].

Outcomes

Our primary outcome was the prevalence of GN carriage, including antibiotic susceptibility. We further determined the proportion of neonates who developed GN BSI by reviewing data on blood cultures performed during hospitalization. Data on BSI and corresponding bacterial isolates were made available through an ongoing prospective study assessing neonatal sepsis at the 2 study sites (clinicaltrials.gov NCT03755635) [14].

Molecular Analysis

All K pneumoniae isolates with phenotypic carbapenemase production were whole-genome sequenced. Deoxyribonucleic acid (DNA) was purified with DNeasy Blood and Tissue kit (QIAGEN, Hilden, Germany). The isolates were sequenced on a MiSeq Instrument (Illumina Inc., San Diego, CA) using paired-end libraries (2 × 250 base pairs). Genome assemblies
were created with VelvOptimiser v2.2.5 and annotated with Prokka v1.12. In silico analyses of resistance genes, MLST and capsular typing were performed using the online platform of the Centre for Genomic Epidemiology of the Danish Technical University and Kaptive applying assemblies [20, 22]. To determine the source of BSI with _K. pneumoniae_, we compared pairs of phenotypically similar isolates (carriage, bloodstream, and environment) in a single nucleotide polymorphism (SNP) analysis using BacDist [23].

**Data Availability**

Raw reads for the 7 _K. pneumoniae_ genomes used in SNP analysis in this study are available in the European Nucleotide Archive (ENA) under the accession number PRJEB37523.

**Statistical Analysis and Definitions**

Data were analyzed with STATA (version 12; StataCorp). Categorical data were compared using χ² test, Z score for proportions, and Wilcoxon rank-sum score for medians. Birth weight <2500 grams was classified as low birth weight. To identify factors associated with carriage of MDRGN as primary outcome and carriage of third-generation cephalosporin resistance as secondary outcome, we generated univariate and multivariate logistic regression models using the purposeful selection of covariates method [24]. We compared neonates with MDRGN with neonates who did not carry MDRGN, which included neonates who did not culture a GN organism. All variables associated with the outcome at a ρ < .2 in univariate analysis were included in multiple regression analysis. This was followed by an iterative process of purposeful removal of covariates in the multiple logistic regression based on their nonsignificance at ρ > .1. Confounders were then removed if they did not change parameter estimate by at least 15%. We present results as crude and adjusted odds ratio (OR) with 95% confidence intervals (CIs). Two-tailed ρ < .05 was considered significant.

**Ethical Considerations**

The study forms part of a larger project on neonatal sepsis given ethical approval by the Institutional Review Boards of KBTH (IRB/0025/2017) and 37MH (37MH-IRB IPN 144/2017). Informed consent was obtained from parents of neonates on admission. For day 1 or fresh admissions, administrative permission was sought to take swabs as part of the admission process. Carriage findings from the study were not disclosed to clinical staff or parents.

**RESULTS**

**Patient Characteristics**

During the 2 periods of sample collection, 228 neonates were assessed for GN carriage. Median duration of stay at time of specimen collection was 3 days (interquartile range [IQR], 1–11). Mortality among the screened neonates was 9.6% (22 of 228). Ninety-two (40.4%) samples were collected on the first day of admission. Table 1 describes the main characteristics of included neonates overall and by hospital.

**Antibiotic Use**

Of the screened neonates, 52% (118 of 228) had received antibiotic treatment before specimen collection. In total, 291 antibiotic prescriptions were made for 118 neonates. The median duration of antibiotic therapy at the time of data collection was 8 days (IQR, 7–12). Most (73%, 86 of 118) had received a combination of 2 (IQR, 2–3) antibiotics. The top 5 antibiotics used were cloxacinill (38.8%, 113 of 291), amikacin (35.4%, 103 of 291), meropenem (8.2%, 24 of 291), ciprofloxacin (6.2%, 18 of 291), and gentamicin (3.1%, 9 of 291) (Figure 1).

**Carriage of Multidrug-Resistant Gram-Negative Bacteria**

A total of 276 GN organisms were isolated from 76.8% (175 of 228) neonates. Table 2 shows common organisms isolated and their respective antibiotic susceptibility patterns. The top 3 organisms isolated were _Klebsiella_ spp (41.7%, 115 of 276), _E. coli_ (26.4%, 73 of 276), and _Enterobacter_ spp (12.3%, 34 of 276).

Overall, the MDRGN carriage rate was 49.6% (113 of 228), whereas carriage of third-generation cephalosporin resistance was found in 46.1% (105 of 228) (Table 2). There was no statistically significant difference in the rate of MDRGN carriage between neonates admitted at KBTH (51.6%, 98 of 190) and 37MH (39.5%, 15 of 38) (P = .20). Multidrug-resistant was most common among _Klebsiella_ spp (87.0%, 100 of 115), followed by _Enterobacter_ spp (70.6%, 24 of 34) (Table 2). For the identified _Klebsiella_ spp, resistance rates were 78.3% (90 of 115) to cefotaxime, followed by 65.2% (75 of 115) to gentamicin and 43.5% (50 of 115) to amikacin. Resistance rates of _E. coli_ were 34.2% (25 of 73) to cefotaxime, 13.7% (10 of 73) to gentamicin, and 1.4% (1 of 73) to amikacin (Table 2).

**Gram-negative bacteria in the environment**

A total of 191 samples were taken from the KBTH NICU environment for culture. Forty sites cultured a total of 47 GN organisms. Fourteen (29.8%) of the organisms were _K. pneumoniae_ from the following sites: incubator doors (4); cots (9); and nurses trolley handle (1). The majority, 85.7% (12 of 14), were MDR, 78.6% (11 of 14) were ESBL positive, and 21.4% (3 of 14) were carbapenemase producing.

**Resistance Mechanisms**

Phenotypic expression of ESBL was found in 76.0% of _Klebsiella_ spp and 32.8% of _E. coli_. Among _Klebsiella_ spp, 16.0% (18 of 115) had meropenem zone <28 mm and were genotypic carbapenemase producers, carrying the carbapenemase _bla_ "OXA-181", as well as ESBL _bla_ "CTX-M-15". Thus, carriage rate of carbapenemase-producing _Klebsiella_ spp was 7.9% (18 of
Carbapenemase-producing organisms were only found at KBTH.

Risk Factors for Carriage of Multidrug-Resistant Gram-Negative Bacteria

Antibiotic administration before specimen collection was associated with carriage of MDRGN in univariate (crude OR, 15.0; 95% CI, 7.9–28.6) and multivariate analysis (adjusted OR [aOR], 11.1; 95% CI, 5.5–22.1) (Table 3). MDRGN carriage was also associated with duration of admission before specimen collection in univariate (crude OR, 1.1; 95% CI, 1.05–1.14) and multivariate (aOR, 1.04; 95% CI, 1.01–1.07) analysis. MDRGN carriage rate increased with duration of hospitalization from 13% for neonates screened at day 1 of admission to 42% by day 2, 47% by day 3, and reached a plateau at 91% by day 15 (Supplementary Figure 2). Carriage of third-generation cephalosporin-resistant organisms was associated with antibiotic use in univariate (crude OR, 16.10; 95% CI, 8.3–31.10) and multivariate analysis (aOR, 12.87; 95% CI, 6.41–25.8). The duration of stay before sampling was also associated with carriage of third-generation cephalosporin-resistant organisms in univariate (crude OR, 1.07; 95% CI, 8.3–31.10) and multivariate analysis (aOR, 1.02; 95% CI, 1.01–1.04) (Table 4). In subgroup analysis of neonates who had received antibiotics, the duration of antibiotic use was significantly associated with carriage of an MDR GN (aOR, 1.16; 95% CI, 1.03–1.30), ie, the odds of carrying an MDR GN increased 1.16 times for each day of antibiotic exposure (Supplementary Table S1). Likewise, duration of antibiotic use was independently associated with carriage of third-generation cephalosporin-resistant organisms among neonates on antibiotics (aOR, 1.19; 95% CI, 1.02–1.41) (Supplementary Table S2). Furthermore, in this subset of patients, low birth weight and vaginal delivery

**Figure 1.** Proportion of antibiotic type prescribed before specimen collection (n = 291).
were independent risk factors for carriage of MDR and third-generation cephalosporin-resistant GN.

**Bloodstream Infections During Admission**

During admission, 7.0% (16 of 228) of the neonates had GN BSI; 13 (81.3%) were MDR, 11 (84.6%) of which were caused by ESBL-producing *K pneumoniae*. Two (18.2%) of the neonates with BSI caused by ESBL-producing *K pneumoniae* were carriers of phenotypically similar organisms. The pairs were ST37/capsular type KL158 and ST37/capsular type KL15. In both cases, BSI had occurred before swabs were taken. Single nucleotide polymorphism analysis of WGS data showed zero SNP difference between each carriage-bloodstream pair of isolates. The ST37 paired isolates (carriage/bloodstream) were closely related genetically to 3 environmental *K pneumoniae* isolated 3 months before admission of the neonate with an SNP difference of 2–8.

**DISCUSSION**

The major finding of this study was a high rate of MDRGN carriage among neonates at 2 NICUs in Ghana. The carriage rate increased with duration of hospitalization and was

### Table 2. Antibiotic Resistance and Resistant Phenotypes Among Neonates With Carriage of Gram-negative Bacteria

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Klebsiella spp N = 115</th>
<th>Escherichia coli N = 73 (%)</th>
<th>Enterobacter spp N = 34</th>
<th>Pseudomonas aeruginosa N = 20</th>
<th>Acinetobacter spp N = 21</th>
<th>Citrobacter spp N = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>115 [100]</td>
<td>54 [74]</td>
<td>34 [100]</td>
<td>-</td>
<td>-</td>
<td>4 [100]</td>
</tr>
<tr>
<td>Amoxiclav</td>
<td>95 [82.6]</td>
<td>34 [46.6]</td>
<td>15 [44.1]</td>
<td>-</td>
<td>-</td>
<td>1 [75]</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>75 [65.2]</td>
<td>10 [13.7]</td>
<td>16 [47.1]</td>
<td>3 [15.0]</td>
<td>11 [52.6]</td>
<td>0</td>
</tr>
<tr>
<td>Amikacin</td>
<td>50 [43.5]</td>
<td>1 [1.4]</td>
<td>14 [41.2]</td>
<td>0</td>
<td>7 [33.3]</td>
<td>0</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>90 [78.3]</td>
<td>25 [34.2]</td>
<td>16 [47.1]</td>
<td>-</td>
<td>-</td>
<td>1 [25]</td>
</tr>
<tr>
<td>Mecillinam</td>
<td>7 [6.1]</td>
<td>1 [1.4]</td>
<td>3 [8.8]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Meropenem</td>
<td>7 [6.1]</td>
<td>0</td>
<td>2 [10.0]</td>
<td>7 [33.3]</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>MDR</td>
<td>100 [87.0]</td>
<td>40 [54.8]</td>
<td>24 [70.6]</td>
<td>3 [15]</td>
<td>7 [33.3]</td>
<td>2 [50]</td>
</tr>
<tr>
<td>ESBL phenotype</td>
<td>87 [75.6]</td>
<td>24 [32.8]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenemase producing</td>
<td>18 [15.6]</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Antibiotic**

- **Klebsiella spp N = 115**
- **Escherichia coli N = 73 (%)**
- **Enterobacter spp N = 34**
- **Pseudomonas aeruginosa N = 20**
- **Acinetobacter spp N = 21**
- **Citrobacter spp N = 4**

**Table 3. Factors Associated With Carriage of Multidrug-Resistant Gram-Negative Bacteria in Neonates Admitted to Neonatal Intensive Care Units**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDR GN Present [n = 113]</th>
<th>Crude Odds Ratio [95% CI]</th>
<th>P Value</th>
<th>Adjusted Odds Ratio [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitting weight (grams)</td>
<td>≥2500</td>
<td>47 [41.6]</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1500–2499</td>
<td>35 [31.0]</td>
<td>1.06 [0.58–1.93]</td>
<td>.854</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1001–1499</td>
<td>24 [21.2]</td>
<td>1.31 [0.65–2.66]</td>
<td>.448</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤1000</td>
<td>7 [6.]</td>
<td>4.02 [0.80–20.31]</td>
<td>.092</td>
<td></td>
</tr>
<tr>
<td>Duration of stay before sample collection (days)</td>
<td>9.0 [4.0–22.0]</td>
<td>1.10 [1.05–1.14]</td>
<td>&lt;.001</td>
<td>1.04 [1.01–1.07]</td>
<td>.023</td>
</tr>
<tr>
<td>Age of mother (years)</td>
<td>29.0 [24.0–35.0]</td>
<td>0.97 [0.93–1.01]</td>
<td>.152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>1.0 [1.0–3.0]</td>
<td>0.83 [0.67–1.03]</td>
<td>.092</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>52 [46.0]</td>
<td>0.68 [0.40–1.16]</td>
<td>.159</td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td>Caesarean section</td>
<td>58 [51.3]</td>
<td>0.78 [0.46–1.32]</td>
<td>.350</td>
<td></td>
</tr>
<tr>
<td>Type of gestation</td>
<td>Preterm</td>
<td>72 [64.9]</td>
<td>1.51 [0.88–2.60]</td>
<td>.133</td>
<td></td>
</tr>
<tr>
<td>Prolonged PROM</td>
<td>Yes</td>
<td>9 [10.4]</td>
<td>3.46 [0.72–16.62]</td>
<td>.121</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; GN, Gram negative; MDR, multidrug-resistant; PROM, premature rupture of membranes.

**Data are presented as medians with interquartile ranges and n/N (%) where appropriate. Significant variables are presented in bold.**
Table 4. Factors Associated With Carriage of Third-Generation Cephalosporin-Resistant Bacteria in Neonates Admitted at Neonatal Intensive Care Units

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3rd-Gen Present</th>
<th>Crude Odds Ratio [95% CI]</th>
<th>P Value</th>
<th>Adjusted Odds Ratio [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitting weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2500</td>
<td>44 [41.9]</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1500–2499</td>
<td>32 [30.5]</td>
<td>1.01 [0.55–1.86]</td>
<td>.972</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1001–1499</td>
<td>22 [21.0]</td>
<td>1.24 [0.61–2.51]</td>
<td>.551</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1000</td>
<td>7 [6.7]</td>
<td>4.53 [0.90–22.91]</td>
<td>.067</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of stay before specimen collection (days)</td>
<td>9.0 [4.0–22.0]</td>
<td>1.07 [1.04–1.10]</td>
<td>.001</td>
<td>1.02 [1.01–1.04]</td>
<td>.044</td>
</tr>
<tr>
<td>Age of mother (years)</td>
<td>29.0 [24.0–35.0]</td>
<td>0.97 [0.93–1.02]</td>
<td>.205</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>1.0 [1.0–3.0]</td>
<td>0.84 [0.68–1.04]</td>
<td>.111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 [44.8]</td>
<td>0.64 [0.38–1.08]</td>
<td>.097</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>55 [52.4]</td>
<td>0.86 [0.51–1.44]</td>
<td>.566</td>
<td>0.95 [0.49–1.83]</td>
<td>.876</td>
</tr>
<tr>
<td>Type of gestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>68 [65.4]</td>
<td>1.54 [0.89–2.65]</td>
<td>.119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged PROMb</td>
<td>Yes</td>
<td>2.31 [0.57–9.06]</td>
<td>.231</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GN, Gram negative; MDR, multidrug resistant; PROM, premature rupture of membranes; 3rd-Gen, third-generation cephalosporin.

Data are presented as medians with interquartile ranges and N (%) where appropriate. Significant variables are presented in boldface.

Statistically significant set at \( P < .05. \)

Table 4. Factors Associated With Carriage of Third-Generation Cephalosporin-Resistant Bacteria in Neonates Admitted at Neonatal Intensive Care Units

The relatively higher rate of OXA-181 in our study could indicate a possible outbreak at the KBTH NICU. On the other hand, the fact that MDR colonization took place within few days of admission in the majority of patients suggests that antimicrobial stewardship and enhanced infection prevention will be critical strategies for the control of MDRGN infections.
Neonatal intensive care units in low-resource settings face the challenge of low staff to patient ratio, limited space resulting in sharing of cots and incubators, and reuse of single-use devices [36]. These practices may facilitate the spread of MDRGN among neonates with the possibility of outbreaks [37]. The high rates of carbapenemase-producing enterobacteriales and ESBLs in the NICUs coupled with previously documented poor hand hygiene practices among healthcare workers in Ghana [38, 39] suggest that these organisms may also spread beyond NICUs if practices are not optimized.

Screening for MDRGN is previously found to be cost intensive, resulting in excess use of antibiotics, and of limited benefit to patients in areas where MDRGN are rare or endemic [3, 10]. Thus, the usefulness of screening in low-resource settings with high prevalence of MDRGN has been questioned [31]. However, in the absence of routine diagnostic microbiology services to inform choice of antibiotics, screening may be useful to design rational empiric treatment policies. The current recommendations suggest that susceptibility to carbapenems should be reported as found in enterobacteriales with OXA-181 [18, 28], but its usefulness in treating such cases remains in doubt [28]. Other agents like colistin or ceftazidime-avibactam combinations may be useful for managing these infections, although the cost may prohibit their use in low-resource settings.

This study has limitations. Specimens were collected at 2 different time periods, and context-specific interventions or events between the periods may have directly affected the carriage rate. In addition, empirical therapy for treating infections varied at both sites. The cross-sectional nature of the study does not allow for proper evaluation of associations between carriage of MDRGN and duration of stay. We also did not have enough neonates who cultured GN organisms that were not MDR for comparison with MDRGN-positive carriage. The carriage rates may have been underestimated because recovery of GN is higher from rectal swabs than from perianal swabs [16], which were used in this study. The study was conducted in tertiary hospitals; thus, our findings may not be generalizable to nontertiary facilities. Nevertheless, this study highlights the role that MDRGN may play in NICUs in LMICs.

CONCLUSIONS

We found high external carriage of MDRGN among hospitalized neonates with high levels of resistance to recommended antibiotics for severe neonatal infections. Carbapenemase production mediated by bla(OXA-181) was found among K pneumoniae. There is a need to improve antibiotic use and infection control and prevention practices in NICUs to limit the potential impact of MDRGN in hospitalized neonates in low-resource settings.

Supplementary Data
Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Supplementary Figure 1A. Proportion of antibiotic type prescribed before specimen collection at KUTH (n = 246).
Supplementary Figure 1B. Proportion of antibiotic type prescribed before specimen collection at 37MH (n = 55).
Supplementary Figure 2. Proportion of multidrug-resistant Gram-negative bacteria compared with days of admission before specimen collection.

Acknowledgments

We acknowledge Mary Magdalene Osei at the Department of Medical Microbiology, University of Ghana Medical School and technical staff at the Department of Microbiology, Rigshospitalaet, Copenhagen for the assistance with laboratory work. We also thank the staff and patients from the participating hospitals for their cooperation during the conduct of the study.


Disclaimer.

The funders had no role in the study design, collection, analysis, and interpretation of data and in writing the manuscript.

Financial support. This work was funded by the Danish Ministry of Foreign Affairs (Grant Number 16-POI-GHA) under the HAI-Ghana project. R. L. M. is funded by the Danish National Research Foundation (Grant Number 126). K. L. N. is funded by MICA foundation.

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


