Resistance Determinants and Factors associated with

Multi-drug Resistant Enterobacteriaceae in Children

BY

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THESIS

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This thesis is dedicated to my wonderful husband Rashaad and our two beautiful children Jaiden and Jovan. Thank you for tolerating all the late nights, weekends, and absences required to accomplish this goal, and for helping me to be a successful student and a physician.

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LIST OF ABBREVIATIONS

AmpC   AmpC Cephalosporinases

Bla   Beta-Lactamases

CRE   Carbapenem-resistant Enterobacteriaceae

CPE   Carbapenemase-producing Enterobacteriaceae

DNA   Deoxyribonucleic acid

ENT   Enterobacteriaceae

ESBL   Extended-Spectrum Beta-Lactamase

ESBL-Ent   Extended-Spectrum Beta-Lactamase-producing Enterobacteriaceae

ESC-R   Extended-Spectrum Cephalosporin Resistant

FQR   Fluoroquinolone resistant

INC   Incompatibility group typing of plasmids

IMP   Active on Imipenem Metallo-beta-lactamase

MBL   Metallo-beta-lactamase

MDR   Multi-drug resistant

MDRO   Multi-drug resistant organism

MLST   Multi-locus sequence type

PMFQR   Plasmid-mediated Fluoroquinolone Resistance

sp.   Species

ST   Sequence type

QRDR   Quinolone Resistance Determining Region

SUMMARY

Multi-drug resistant (MDR) Enterobacteriaceae infections are associated with significant morbidity and mortality and are an emerging problem in children. Globally, this has been mainly attributed to the rise in extended-spectrum beta lactamase (ESBL) producing Enterobacteriaceae (ESBL Ent) and carbapenemase-producing Enterobacteriaceae (CPE). National studies have found an increase in MDR Enterobacteriaceae infections in children over the last decade; however, there is a paucity of literature on the antibiotic resistance determinants associated with these increases, and, regarding the children most impacted by these dangerous pathogens.

In the first objective of the study, we first used a retrospective cohort study design to survey the resistance determinants associated with MDR Enterobacteriaceae infections in children cared for at five centers in the Chicago metropolitan area, an endemic region, using several molecular techniques. The second objective was to perform an analysis on a subgroup of infections with similar resistance determinants (plasmid-mediated fluoroquinolone resistance and extended-spectrum beta-lactamase resistance); to determine the children with increased odds for these infections. To accomplish this, we used a case-control study design comparing children with antibiotic-resistant infections to those with antibiotic-sensitive infections in order to determine factors associated with infection due to our phenotype of interest. We used logistic regression for multivariable analysis.

Of 276 Enterobacteriaceae isolates from unique children (ages 0-19 years) phenotypically identified as ESBL Ent or CPE, 64% were *Escherichia coli* and 69% were recovered from the urine. The median age of the overall population was 4.8 years, 59% were female, and 46% were not hospitalized (outpatient clinics or emergency department) at the time of infection. The most

SUMMARY (continued)

common beta-lactamase (*bla*) gene detected was the $bla_{CTX-M-1group}$ (49%) and 1.4% were CPE, although complex *bla* genotypes were associated with the ESBL and carbapenemase phenotypes.

Additionally, plasmid mediated resistance to the fluoroquinolone antibiotics, antibiotics uncommonly used in children, was found in 56 of 82 (62%) isolates tested. We chose to further analyze this population because of its uniqueness; an effort to understand which children had a higher likelihood of infections with organisms which were resistant to both beta-lactam antibiotics and fluoroquinolone antibiotics. In adults, fluoroquinolone resistance in isolates additionally resistance to beta-lactams has been commonly linked with chromosomal resistance mechanisms rather than plasmid-based mechanisms. We performed a case-control study to assess factors associated with these specific infections.

On multivariable analysis, when comparing children with plasmid-mediated fluoroquinolone Enterobacteriaceae (PMFQR Ent) infections to those with Enterobacteriaceae infections that were antibiotic sensitive or treatable by cephalosporins and fluoroquinolones (matched by age, hospital and source of infection), residence in southwest Chicago and the southwest suburban region (OR 5.3; 95%CI 1.8, 15.2; p=0.002); race "other" non-white, non-black, non-Hispanic (OR 6.5; 95%CI 1.9, 22.2; p=0.003) and infection diagnosed in the outpatient setting (OR 33.1; 95%CI 7.1, 154.7; p<0.001) were associated with PMFQR Ent infection. Residence in the downtown Chicago region was negatively associated with PMFQR Ent infection (OR 0.03; 95%CI 0.002, 0.3; p=0.004) after controlling for race and location at time of diagnosis. We did not find any differences in organisms, comorbidities, antibiotic exposures, or presence of devices between groups after controlling for other variables.

SUMMARY (continued)

We identified that there is complexity and diversity in genetic determinants associated with multi-drug resistance in Enterobacteriaceae isolates from children. We additionally revealed that there are regional differences in the likelihood of infection with MDR Enterobacteriaceae within the Chicago metropolitan area based on residence of children, and that a significant proportion of infections are identified in the community. This may reflect linkage to bla_{CTX-M} harboring plasmids which are endemic in some communities. Further studies are necessary to assess environmental and other influences associated with regional differences in acquisition of these dangerous pathogens. This is critical to inform prevention strategies in a vulnerable population.

I. INTRODUCTION

A.   <u>**Background**</u>

Antibiotic-resistant bacterial infections are a rapidly growing concern and represent a major public health threat in the United States and worldwide (1). While antibiotic-resistant bacteria have been in existence for millions of years, these organisms were most often restricted to the environment. What has led to resistance in bacteria becoming a significant health issue over the past 70 years is the selective pressure generated by the broad use of antibiotics in agriculture, livestock, veterinary and human medical practices (2). The result has been a dramatic expansion of multi-drug resistant organisms (MDROs) in all persons, including children, and these MDROs are associated with significant morbidity and mortality in affected individuals (3).

These alarming trends of increasing antibiotic resistance are highlighted in Enterobacteriaceae, a family of gram-negative bacteria (GNB) known to cause a variety of infections acquired in both the community and healthcare settings (4). The major driving force of antibiotic resistance in GNB are the beta-lactamases, enzymes encoded by beta-lactamase (*bla*) genes which are able to hydrolyze or break down beta-lactam antibiotics (5). Originally these beta-lactamase genes were narrow spectrum and chromosomally-based; however, the current pandemic of beta-lactamase-producing Enterobacteriaceae is due to the rapid increase in the transmission of broad-spectrum beta-lactam resistance via horizontal gene transfer. Notable mobile genetic elements involved in the transmission of resistance include plasmids, transposons, integrons, insertion sequences, and integrative conjugative elements (6, 7).

The beta-lactams are a diverse class of antibiotics with broad activity against many pathogens, and are divided into four subgroups, namely, the penicillins, the cephalosporins, the monobactams, and the carbapenems. Transmissible genes in Enterobacteriaceae encoding extended-spectrum β-lactamases (ESBLs) yield resistance to penicillins, cephalosporins, and monobactam antibiotics, while Enterobacteriaceae with the additional ability to break down carbapenems, known as carbapenem-resistant Enterobacteriaceae (CRE), often carry carbapenemase genes (5). The most common circulating ESBL-producing Enterobacteriaceae (ESBL-Ent) and carbapenemase-producing Enterobacteriaceae (CPE) strains in the U.S. are the multi-locus sequence type 131 (ST131) CTX-M-ESBL harboring *Escherichia coli*, and the clonal group 258 (CC258) Klebsiella pneumoniae carbapenemase (KPC)-producing *Klebsiella pneumoniae*, of which most often belong to sequence type (ST) 258. These strains are often MDROs, with additional resistance genes to other important antibiotic classes used in the treatment of Enterobacteriaceae including aminoglycosides, fluoroquinolones, tetracyclines, and trimethoprim-sulfamethoxazole (8, 9).

Other notable beta-lactamase genes which produce an extended-spectrum cephalosporin resistant phenotype are the AmpC cephalosporinases (AmpC). AmpC resistance may be plasmid based or chromosomally mediated in Enterobacteriaceae. Plasmid based AmpC genes are less common than ESBL genes in Enterobacteriaceae, and are more commonly found in *E. coli* than other species (10). Within CPE, another important group are the metallo-beta-lactamases (MBL), which have carbapenemase genes harbored by plasmids, transposons, and integrons. MBL Ent are frequently resistant to 3 or more classes of antibiotics, referred to as multi-drug resistant (MDR) (11). Furthermore, CPE are capable of rapid dissemination and spread (12). The most notable transmissible MBL genes globally include IMP (active on Imipenem), NDM (New Delhi

MBL) and VIM (Verona integron encoded MBL) (12, 13). Enterobacteriaceae not uncommonly harbor more than one beta-lactamase gene (13, 14).

In prior work, we used phenotypic, antimicrobial susceptibility data reported to approximately 300 laboratories participating in The Surveillance Network (TSN, Eurofins-Medinet, Herndon, VA) to assess antibiotic resistance trends in Enterobacteriaceae recovered from children in each of nine U.S. Census Bureau regional divisions between the years of 1999-2012 (15, 16). In these studies, there was a significant increase in extended-spectrum cephalosporin-resistant Ent, ESBL Ent and CRE infections in U.S. children over the time period. Additionally, increasing resistance to several other classes of antibiotics was noted, including to fluoroquinolones, a class of antibiotics with limited indications for use in children (15, 16). Resistance to fluoroquinolones is due to both chromosomal and plasmid based mechanisms, and high levels of resistance are seen in bacterial isolates where both resistance mechanisms are active (17).

The reasons for these increases in antibiotic resistance in children are unclear, as genotypic studies assessing the resistance determinants associated with the MDR phenotype in Enterobacteriaceae recovered from children are limited. Additionally, the majority of published data assessing factors associated with MDR Enterobacteriaceae infections in children have been mostly limited to single center studies, and no other U.S. studies prior to our work have been multi-centered studies assessing factors associated with MDR Enterobacteriaceae infection in children treated by different medical centers within a single metropolitan locale.

B.   Study Objectives

Our first study objective was to determine the genetic basis of ESBL, carbapenem, and fluoroquinolone resistance (FQR) phenotypes in Enterobacteriaceae isolates from children cared for by multiple centers in the Chicago area. This survey will improve scientific knowledge on the genetic composition of antibiotic-resistant bacteria in children from varying backgrounds and settings within a large metropolitian area. Our second study objective was to identify which exposures and host factors serve as predictors of infection within dominant genotypes of resistant Enterobacteriaceae recovered from children from multiple centers.

Understanding the genotypes, host factors, and exposures leading to infection with MDR Enterobacteriaceae strains allows us to best identify means of acquisition, as well as to identify the children at highest risk for infection. This is an important first step to inform preventive and surveillance strategies, and ultimately, to formulate prospective studies and interventional trials in high risk populations.

II. METHODS

A. Study Setting

Hospital A contains a 115-bed children's hospital within a tertiary care academic medical center which has a mother-newborn infant unit, pediatric and psychiatric wards, and cardiac, pediatric and neonatal intensive-care units (PICU and NICU). Hospital B has 288 beds and is a free-standing children's academic medical center. Hospital B provides complex quaternary services, such as pediatric organ and bone marrow transplantation. Hospitals C, D, and E are 125-bed, 138-bed and 98-bed, respectively, and are children's hospitals within academic medical centers. Each hospital has a general pediatrics and newborn infant wards, as well as a PICU and NICU. All of the participating centers are within the metropolitan Chicago.

B. Study Design

I. Descriptive Study Design

A. Study Population

This survey included patients aged 0 to 18.99 years with a culture containing an organism (in the family Enterobacteriaceae) found to have an extended-spectrum cephalosporin resistant (ESC-R) or carbapenem-resistant (CR) phenotype, and laboratory testing consistent with presence of a beta-lactamase gene. Additionally, isolates found to be resistant to fluoroquinolones (FQR) were further characterized. Infections were diagnosed between January 1, 2011 and December 31, 2015. Each isolate was included only if from distinct patients. Institutional review board approval was obtained by investigators at the five participating institutions. Centers began participating in at various times during the study period (Figure 1).

FIGURE 1

Timeline for beginning of isolate collection at participating centers, by year

Hospital A Hospital B	Hospital C			Hospital D Hospital E
↓	↓			↓
2011	**2012**	**2013**	**2014**	**2015**
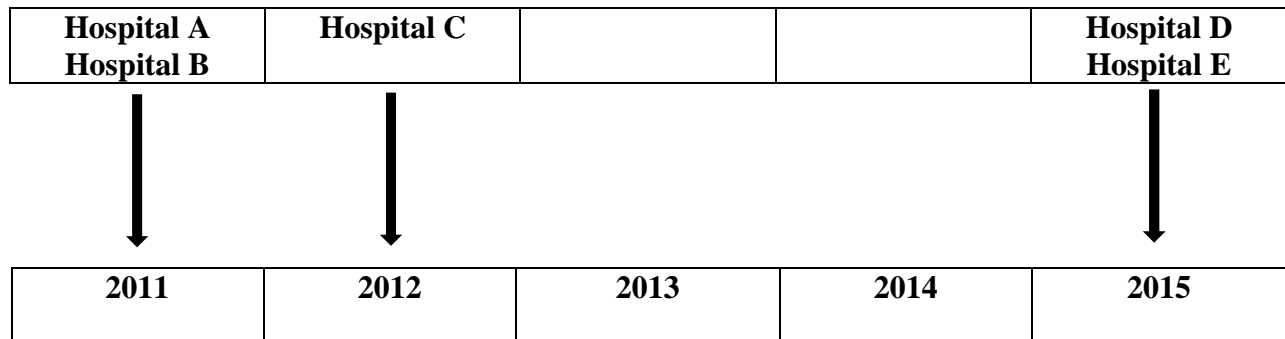
B. Testing of Antibiotic Susceptibility in Enterobacteriaceae

The Hospitals A-E microbiology laboratories phenotypically analyzed presumed ESBL Ent, AmpC Ent and CPE isolates via the Vitek 2 microbial identification system (*bioMérieux, Athens, GA*) or by the MicroScan WalkAway system (Siemens Healthcare Diagnostics, Tarrytown, NY). The screening of beta-lactams for the production of ESBL involved any testing with one or more of the following agents: aztreonam, ceftazidime, ceftriaxone, cefotaxime or cefpodoxime; this is based on the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (18). ESBL production was confirmed on the automated instruments or disk diffusion assays (BBL; Becton, Dickinson and Company, Sparks, MD) or by measuring minimum inhibitory concentrations (MICs) of ceftazidime and cefotaxime in the presence or absence of clavulanic acid. A measurement of an increase in disk zone diameter of > 5 mm or a 4-fold reduction in the MIC of ceftazidime or cefotaxime when combined with clavulanic acid (versus the MIC of the antibiotic) served as confirmation of the ESBL phenotype (18).

The carbapenemase phenotype was determined by Centers for Disease Control and Prevention (CDC) criteria; isolates that were non-susceptible to all extended-spectrum cephalosporins (cefotaxime, ceftazidime, or ceftriaxone), and resistant to one or more carbapenem (imipenem, meropenem, doripenem, or ertapenem) (19). Carbapenemase production was phenotypically confirmed by MBL E-test (bioMérieux, Athens, GA) or Modified Hodge Test, as appropriate (20, 21).

C. Determination of Beta-Lactam Resistance Mechanisms

Genomic DNA was extracted and purified from isolates using the DNeasy Blood & Tissue Kit (QIAGEN, Inc., Valencia, CA). To evaluate for the presence of *bla* genes in isolates, a DNA microarray based assay was performed (Check-Points, Check-MDR CT101 kit; Wageningen, The Netherlands). The CT101 microarray based assay is able to detect the following *bla* groups: CTX-M-1 group, CTX-M-2 group, CTX-M-8 and -25 group, CTX-M-9 group, SHV WT and SHV-type ESBL, TEM wild-type, and TEM-type ESBL, plasmid based AmpC cephalosporinases (pAmpC) (CMY II, ACC, FOX, DHA, ACT/ MIR) and carbapenemases (KPC and NDM-1) (22). When isolates were found *bla* negative by the CT101 assay, a broader DNA microarray, (Check-Points, Check-MDR CT103XL kit) was performed. The CT103XL assay is able to detect the presence of additional ESBL genes (VEB, PER, BEL, GES) and carbapenemase genes (GES, GIM, IMP, SPM, VIM, and OXA-23, -24, -48, and -58) (23). The assays were performed per manufacturer's protocol and as described in preliminary studies (24).

D. Analysis of Determinants Yielding Fluoroquinolone Resistance

To investigate the presence of FQR determinants in MDR Enterobacteriaceae isolates, we evaluated FQR by analyzing the quinolone resistance-determining region (QRDR) located on the bacterial chromosome, and assessed for plasmid-mediated quinolone resistance (PMFQR) in strains found FQR by CLSI standards (18). Briefly, mutations in *gyrA* and *parC* genes of the QRDR and the detection of PMFQR are performed by deoxyribonucleic acid (DNA) sequencing of amplicons and by polymerase chain reaction (PCR) (17). Extraction of genomic DNA followed by amplification and sequencing were performed using primers and methods as previously described by our laboratory and others (25-27). Specific PMFQR genes screened include *qnrA, qnrB, qnrD, qnrS, qepA*, *oqxA* and *oqxB* and *aac6'-Ib-cr* and represent transmissible types previously reported in Enterobacteriaceae (28) .

E. Multilocus Sequence Typing (MLST)

Per protocol, eight *E. coli* housekeeping genes for (*dinB, icdA, pabB, polB, putP, trpA, trpB and uidA*) and seven *Klebsiella* species (sp.) housekeeping genes *(rpoB, gapA, mdh, pgi, phoE, tonB, infB)* were amplified and sequenced as in prior studies (24, 29, 30). Sequence types (ST) and alleles were assigned on select isolates of varying genotypic profiles by MLST Pasteur scheme (http://www.pasteur.fr/recherche/genopole/PF8/mlst/).

F. Analysis of Plasmid Replicon Types and Phylogenetic Grouping

E. coli were assigned to four major phylogenetic groups (A, B1, B2 and D) using a well-established multiplex PCR-based method (31). Plasmids were typed (in select isolates with

varying genotypic profiles) based on incompatibility group corresponding to the nomenclature assigned by Carattoli *et al*. (32).

II. Analytic Study Design

A. Study Groups

We used a retrospective case–control study design to assess factors associated with infection due to fluoroquinolone resistant (FQR) isolates. Bacteria were molecularly characterized as previously described in the first objective. We chose to further analyze fluoroquinolone resistance as this class of antibiotics is uncommonly used in children, yet 50% of the isolates between 2011 and 2014 were found to be FQR. The case group of children had the resistant bacterial phenotype of interest (FQR), in addition to beta-lactam resistance. The case population included children infected with an Enterobacteriaceae resistant to beta-lactams and fluoroquinolones (FQR Ent) between January 1, 2011 and December 31, 2014 in which we had fully molecularly characterized isolates and detected a PMFQR gene.

We selected as controls, children with infections due to bacteria susceptible to the antibiotics of interest during the same period. Specifically, the control group included children with infections that were susceptible to extended-spectrum cephalosporin, carbapenem and fluoroquinolone antibiotics in order to best understand differences between children who acquire plasmid-mediated MDR Enterobacteriaceae infections and those who do not. We hypothesized that fluoroquinolone resistance would be both plasmid and chromosomally mediated, and that acquisition of plasmid-mediated fluoroquinolone resistance in children would have environmental influences and community origins. Therefore, we anticipated finding differences in acquisition of PMFQR by geographical area.

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Only infected patients (versus colonized patients) were included, and infection versus colonization was determined by study investigator case review and/or using standard criteria defined by the CDC National Healthcare Safety Network (33). Children serving as control subjects were identified using hospital electronic laboratory records (ELRs). Control patients were matched approximately 3:1 to the cases by age range, hospital, and specimen source. The control subjects were distinct patients from those included in the case group.

B. Covariates

Several variables were analyzed as potential factors associated with FQR Ent infection based on known associations for acquisition in adults including (1) demographics (age, gender, race/ethnicity); (2) comorbid conditions (as defined by ICD-9 codes); (3) recent inpatient and outpatient healthcare exposures, including hospitalization and/or procedures in the previous 30 days; (4) all recent antibiotic exposures in the 40 days prior to culture; (5) presence, number, and type of invasive medical devices; and (6) the impact of location of patient residence in the Chicago area was assessed by dividing the metropolitan area into 7 regions which included Chicago proper and its suburban areas (i.e. Northwest side and Northwest Suburbs, Southwest side and Southwest Suburbs, etc.). An eighth region included patients from other parts of Illinois or from other states. See Table VI, Appendix A for breakdown of residential regions by zip code.

C. Statistical Analysis

First, the groups were examined for differences using chi-squared tests for categorical, and analysis of variance for continuous variables. When significant differences were discovered, Fisher's exact and Wilcoxon rank sum tests were analyzed as appropriate. $P \leq 0.05$ was considered statistically significant unless otherwise specified. Variables with $p < 0.1$ on bivariate analysis were included in multivariable analysis. Stepwise multiple logistic regression was used to assess the multivariable relationship between the covariates and the groups. Briefly, starting with a null model where each variable is considered univariately, the variable with the smallest p-value was added to the model and the remaining variables were reassessed one at a time. The procedure is repeated until there are no more statistically significant covariates ($p < 0.05$). The final multivariable logistic regression model included the simplest model with significant covariates from the stepwise selection process, and PMFQR Ent infection as the outcome variable. The simplest model was chosen based on a relatively small sample size and the effect of variables in the model. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

III. RESULTS

A. Description of Overall Study Population of Children and Enterobacteriaceae

1. Characteristics of Children in the Overall Study Population

During the study period, 276 ESBL-, AmpC-, or carbapenemase-producing Enterobacteriaceae infections occurred in pediatric patients. The median age of the children was 4.8 years (range 0.008 – 18.9 years); 27% were infants under the age of one year (Table I). The majority of children (56%) of the female gender, 36% were of Hispanic race, and 46% of patients were located in the outpatient setting (primary care and specialty clinical offices or emergency departments) at the time diagnosis.

2. Characteristics of Bacteria in the Overall Study Population

Of the 276 bacteria, 62.3% were *E. coli*, 15.6% were *Klebsiella* sp., 12.7% were *Enterobacter* sp., 5.8% were *Proteus mirabilis*, 2.9% were *Serratia marcescens*, and 0.8% were other (including *Citrobacter* sp. and *Morganella* sp.). Urine was most common specimen source (69.6%); 14.9% were recovered from respiratory sources (bronchoalveolar lavage, sputum, or tracheal aspirate), 5.1% were blood, 4.7% were abscesses or wounds, 2.2% were abdominal and/or peritoneal sources, 0.4% were central nervous system, and 2.9% were other sources.

3. Antibiotic Susceptibilities of Bacterial Isolates

The antibiotic susceptibilities of available isolates revealed that the carbapenems (meropenem and imipenem) and the aminoglycoside amikacin remained the most active against isolates, with 98.2% of Enterobacteriaceae sensitive to imipenem or meropenem and 97.1% were sensitive to amikacin. A high proportion of urinary isolates (82.2%) retained susceptibility to nitrofurantoin. The bacteria had significant resistance to the other aminoglycosides including

gentamicin (56%) and tobramycin (45%), as well as to other classes. Sixty percent of isolates

were resistant to trimethoprim/sulfamethoxazole and 51% were resistant to the fluoroquinolones

(ciprofloxacin and levofloxacin). The MDR phenotype was present in 60% of isolates.

TABLE I

DEMOGRAPHICS OF CHILDREN DIAGNOSED WITH ESBL-, AMPC-, OR
CARBAPENEMASE-PRODUCING ENT INFECTIONS

Demographic variable	N= 276
Median age, years (range)	4.8 (0.008 – 18.9)
Age < 1 years	75(27)
Male	120(43)
Race/Ethnicity	
Hispanic	99(36)
Caucasian	71(32)
Black	47(17)
Other	48(17)
Healthcare Location	
Outpatient Clinic	76(28)
PICU	67(24)
Pediatric Ward	67(24)
Emergency Department	50(18)
NICU	16(6)

[a]Values represent n (%) unless otherwise indicated.

4. Composition of Beta-Lactamase (*bla*) Genes in Enterobacteriaceae

Table 2 summarizes the beta-lactamase genes identified by the Check-Points DNA

microarray analysis. Of the 276 isolates, 86.6% harbored at least one *bla* gene, and in some

isolates more than one *bla* was found (272 *bla* genes were detected in 239 bacteria). The most

common *bla* genes identified were the CTX-M-type ESBLs, discovered in 180 of 276 (65.2%) isolates. Almost half, (49.3%), of *bla* genes detected were $bla_{CTX-M-1\ group}$, which includes $bla_{CTX-M-15}$, the *bla* gene associated with the pandemic CTX-M *E. coli* strains (34, 35). Additionally, bla_{TEM} and $bla_{SHV-type}$ ESBL genes were in 5.1% and 14.3% of isolates respectively. No isolates harbored $bla_{PER-type}$ or $bla_{VEB-type}$ ESBLs.

Genes producing AmpC cephalosporinases in isolates were also assessed using the Check-Points DNA microarray system, and bla_{AmpC} cephalosporinase genes comprised 34/272 (12.5%) of the resistance determinants detected, of which 7 (2.6%) were bla_{CMY} genes and 27 (9.9%) were $bla_{ACT/MIR}$ AmpC genes. The bla_{CMY} genes were mainly detected in *E. coli* (6 of 7); by contrast, of the 27 ACT/MIR genes, the majority (85.2%) were identified in *Enterobacter* sp. with only 14.8% found in *E. coli* isolates. *Enterobacter* sp. isolates harboring $bla_{ACT/MIR}$ genes commonly also carried bla_{SHV} ESBL genes, 13/23 (57%). The presence of both bla_{ESBL} and bla_{AmpC} genes were found in 14 of 34 (41%) *Enterobacteriaceae* isolates. We did not find bla_{AmpCs} in *Serratia* or *Proteus* sp.; however a $bla_{CMY-like}$ gene was detected in a single *Citrobacter freundii*, which represented an intrinsic chromosomal bla_{AmpC} gene known to be specific to *Citrobacter* sp. This was confirmed by DNA sequence analysis.

Carbapenemase genes were harbored by 5 organisms (1.8%), 4 of which contained a bla_{KPC} and 1 *K. pneumoniae* harbored a bla_{IMP} MBL gene. The bla_{KPC} genes were detected in three *K. pneumoniae* and one *E. coli*. Three of the bla_{KPC} genes were identified as bla_{KPC-2} by DNA sequencing with one *K. pneumoniae* harboring a bla_{KPC-3} gene. No carbapenemase-containing isolates harbored more than one *bla* gene.

TABLE II

BETA-LACTAMASE (*bla*) GENES IN PEDIATRIC ENTEROBACTERIACEAE

Beta-lactamase genes in isolates	% *bla* gene detection by organism						
(n)	All (276)	*E.coli* (172)	*Klebsiella sp.*(43)	*Enterobacter sp.*(35)	*Proteus sp.*(16)	*Serratia sp.*(8)	Other (2)
ESBL Genes (233)	%	%	%	%	%	%	%
CTX-M-1 grp (134)	49.3	82.1	11.2	3.0	3.7	0.0	0.0
CTX-M-9 grp (43)	15.8	86.0	9.3	2.3	2.3	0.0	0.0
CTX-M-2 grp (3)	1.1	33.3	33.3	0.0	33.3	0.0	0.0
TEM (14)	5.1	57.1	7.1	7.1	28.6	0.0	0.0
SHV (39)	14.3	17.9	28.2	41.0	0.0	12.8	0.0
VEB (0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PER (0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AmpC genes (34)							
ACT/MIR (27)	9.9	14.8	0.0	85.2	0.0	0.0	0.0
CMY (7)	2.6	85.7	0.0	0.0	0.0	0.0	14.3[c]
Carbapenemase genes (5)							
KPC (4)	1.4	25.0	75.0	0.0	0.0	0.0	0.0
IMP (1)	0.4	0.0	100	0.0	0.0	0.0	0.0
Total genes detected (272)							

[a]Some isolates contained > 1 *bla* gene; in 13.4% (37) of isolates no *bla* gene was detected.
[b]Narrow-spectrum or wild type *bla* genes have not been included in the analysis or totals.
[c]Represents a chromosomal bla_{CMY} copy specific to *Citrobacter* sp. (intrinsic gene).

5. Multilocus Sequence Typing and Plasmid Replicon Typing

A subset of isolates based on beta-lactamase detected and fingerprint patterns were

characterized by DNA sequencing, plasmid replicon typing, and MLST, and the majority were

related to the pandemic ST43 strains by the Pasteur MLST nomenclature (ST131 by Acthman's

MLST nomenclature), to harbor $bla_{CTX-M-15}$, and to be propagated by plasmids found to be incompatibility types of replicon FIA, FII, and FIB. The bla_{KPC-2} harboring *E. coli* was of phylogenetic group D and was discovered to be of a novel sequence type, ST701.

Concerning *K. pneumoniae*, most fingerprint profiles were unrelated and plasmid replicon typing revealed that of the KPC-producing *K. pneumoniae,* those carrying bla_{KPC-2} were associated with plasmid replicon types I1 and A/C, and did not belong to the pandemic ST258 lineage (ST22 and ST29); whereas the bla_{KPC-3} producing *K. pneumoniae* was found to belong to the ST258 lineage and the bla_{KPC-3} was carried on a transposon, *Tn*4401. The *K. pneumoniae* harboring the bla_{IMP} gene was identified as a bla_{IMP-13} carried by strain ST253, an uncommon sequence type.

6. Phylogenetic Grouping of *E. coli*

There are four main phylogenetic groups of *E. coli* (A, B1, B2, and D), and groups B2 and D contain several virulence factors that are clinically associated with severe disease (31). Of 170 *E. coli* tested, 146 (85.9%) were of phylogroup B2 or D, with 65.3% and 20.6% being B2 and D, respectively. The majority of *E. coli*, 110/170 (64.7%) were linked with $bla_{CTX-M-1}$ group, of which 70% were phylogroup B2 and 14% were phylogroup D; 21.8% of *E. coli* were linked with $bla_{CTX-M-9}$ group. Most (77/110, 70%) were phylogroup B2 *E. coli* carrying $bla_{CTX-M-1}$ genes, with D-, A-, and B1-*E. coli* harboring $bla_{CTX-M-1}$ group genes representing 14%, 14%, and 3%, respectively. Only 20 (11.8%) and 4 (2.4%) of *E. coli* strains were of the less virulent phylogroups A and B1, respectively.

B. Analysis of Resistance Mechanisms and Factors associated with Plasmid-Mediated Fluoroquinolone Resistance in Children

1. Composition of Fluoroquinolone Resistance (FQR) Genes in Enterobacteriaceae

We assessed 169 *bla*-producing Ent isolates between 2011 – 2014 from Hospitals A, B, and C for the presence of FQR (Table III). Of 169 Ent isolates, 85 (50%) were FQR of which 82 (96.4%) were available for further testing. The median age of children with FQR-Ent infections was 4.8 years. The predominant organism was *E. coli*, 65/82 (79%), and the predominant *bla* genotype found associated with FQR in Ent was $bla_{CTX-M-1}$ group in 62% of cases. Within *E. coli*, FQR was most often associated with phylogroup B2 and ST43/ST131 harboring $bla_{CTX-M-1}$ group in 47/63 (75%) cases.

FQR isolates were further characterized to understand resistance determinants associated with FQR in pediatric Ent isolates. Chromosomal mutations of the QRDR (*gyrA*/*parC*) were present in 71/79 (89.9%) of FQR isolates by DNA sequence analysis. Three isolates did not yield results. Plasmid-mediated FQR (PMFQR) genes were detected by PCR in 56/82 (66%); 53 (95%) were available for further analysis. The median age was 6 years. PMFQR gene mutations included *aac 6'1b-cr*, *oqx A/B*, *qepA*, and *qnr A/B/D/S* in 83%, 15%, 13% and 11% of isolates, respectively. PMFQR was found in combination with *gyrA* and/or *parC* mutations in 43/49 (88%) isolates, which is associated with high level resistance. The predominant *bla* genotype found associated with PMFQR was $bla_{CTX-M-1}$ group in 76%, followed by $bla_{SHV\ ESBL}$ associations in 11%. Almost all (98%) of PMFQR Ent were multi-drug resistant.

TABLE III

CHARACTERISTICS OF FQR AND PMFQR ENTEROBACTERIACEAE

Variable	FQR Ent	PMFQR Ent
Organism	n=82	n=53
E. coli	65 (79.3)	40 (75.5)
Klebsiella sp.	7 (8.5)	7 (13.2)
Proteus sp.	7 (8.5)	4 (7.5)
Enterobacter sp.	3 (3.7)	2 (3.8)
Other	0(0)	0 (0)
Source		
Urine	58 (70.7)	37 (69.8)
Respiratory	12 (14.6)	7 (13.2)
Abscess/Wound	4 (4.9)	3 (5.7)
Blood	3 (3.7)	3 (5.7)
Peritoneal/Abdomen	2 (2.4)	1 (1.9)
Central Nervous System	1 (1.2)	1 (1.9)
Other	2 (2.4)	1 (1.9)
Co-Antibiotic Resistance		
Trimethoprim/Sulfamethoxazole	59 (72.0)	38 (71.7)
Gentamicin	44 (53.7)	35 (66.0)
Amikacin	3 (3.7)	3 (5.7)
Carbapenem	1 (1.2)	1 (1.9)
Bla gene association [b]		
$CTX-M-1_{group}$	51 (62.2)	42 (79.2)
$CTX-M-9_{group}$	13 (15.9)	3 (5.7)
SHV_{ESBL}	9 (11.0)	6 (11.3)
VEB_{ESBL}	1 (1.2)	1 (1.9)
CMY_{AmpC}	2 (2.4)	1 (1.9)
ACT/MIR_{AmpC}	4 (4.9)	1 (1.9)
KPC_{CRE}	1 (1.2)	1 (1.9)
Mutation in QRDR [c]	71 (89.9)	43 (87.8)
Phylogenetic group of *E. coli*	n=65	n=40
B2	49 (75.4)	31 (77.5)
D	11(16.9)	6 (15.0)
A	4 (6.1)	3 (7.5)
B1	1 (1.5)	0 (0)

[a]Values represent n (%).

[b] Isolates may harbor one or more *bla* gene.

[c] 3 of the 82 isolates did not yield a result, calculation based on 79 isolates.

2. Analysis of Factors Associated with PMFQR Enterobacteriaceae Infections in Children

Cases of PMFQR Ent infection were matched by age, hospital, and source to controls with antibiotic sensitive Ent infections as previously described. Significant factors associated with PMFQR Ent infection on uni- and bivariate analysis included: having an *E. coli* infection, race/ethnicity, having the infection diagnosed in the outpatient clinic, history of quinolone use, and residence in the southwest "high risk" region, comprised of southwest Chicago and the southwestern Chicago suburbs (Table IV). Children with PMFQR infection were less likely to have infection with *Enterobacter* sp., a central venous catheter, admitted to the neonatal intensive care unit at the time of infection diagnosis, and less likely to reside in the "low risk" region (comprised of the downtown Chicago area, near North side, Chicago loop, and North Chicago). There were no differences in comorbid conditions, having respiratory, gastrointestinal, or genitourinary foreign bodies, or the overall presence of foreign bodies, or recent health care exposure between groups.

We did not find evidence of significant effect modification during the model building stages. We additionally did not find evidence of significant confounding and therefore no additional covariates were added back to the final model after the stepwise selection process was completed, and the simplest model was used in the final regression model.

TABLE IV

BIVARIATE ANALYSIS OF DEMOGRAPHICS AND FACTORS ASSOCIATED
WITH PMFQR ENTEROBACTERIACEAE INFECTION

Characteristic[a]	PMFQR Infection (n=53)	Non-PMFQR Infection[b] (n=131)	p value
Location at Diagnosis			<0.0001
Inpatient, non ICU	21 (39.6)	46 (35.1)	
Outpatient Clinic	16 (30.2)	7 (5.3)	
Emergency Room	4 (7.6)	23 (17.6)	
Pediatric ICU	11 (20.8)	37 (28.2)	
Neonatal ICU	1 (1.9)	18 (13.7)	
Region of Residence[d]			0.047
Downtown	1 (1.9)	19 (14.5)	
Northwest	6 (11.3)	14 (10.7)	
Far North	14 (26.4)	25 (19.1)	
West	12 (26.4)	36 (27.5)	
Southwest	10 (18.9)	8 (6.1)	
South	2 (3.8)	12 (9.2)	
Far South	3 (5.7)	8 (6.1)	
Other IL/Other states	3 (5.7)	9 (6.9)	
Recent Health Care			0.406
Inpatient Care	12 (22.6)	31 (23.7)	
Outpatient Care[e]	31 (58.5)	64 (48.9)	
No Recent Care	10 (18.9)	36 (27.5)	
Central venous line	9 (17.0)	44 (33.6)	0.025
Gastrointestinal	13 (24.5)	45 (34.4)	0.195
Genitourinary	14 (26.4)	37 (28.2)	0.802
Respiratory	11 (20.8)	38 (29.0)	0.253

[a] Values represent n (%) unless otherwise indicated.

[b] Non-PMFQR Infection were children with infections due to Enterobacteriaceae sensitive to extended spectrum cephalosporin and fluoroquinolone antibiotics.

[c] Other sources include abscess/wound, peritoneal/abdomen, or other organ systems

[d] Region of residence includes city region and neighboring suburbs, except for "Downtown", which includes downtown, near North side, loop, and Northside, all within city limits. "Other" includes other cities in Illinois not neighboring Chicago, and patients from other states.

[e] Includes extended-spectrum cephalosporins (ceftriaxone, ceftazidime, cefotaxime, cefepime)

[f] Abbreviation TMP-SMX, Trimethoprim-Sulfamethoxazole.

[g] Outpatient care includes care outside of routine child care visits and outpatient procedures.

On multivariable analysis (Table V), having infection diagnosed in the outpatient clinic setting was significantly associated with PMFQR Enterobacteriaceae infection (OR=33.1; 95% CI 7.1, 154.7; p<0.001). Being of a race or ethnicity other than white, black, or Hispanic was also significantly associated with PMFQR Enterobacteriaceae infection (OR 6.5; 95% CI 1.9, 22.2; p=0.003). Interestingly, we also found that among children with Enterobacteriaceae infections, those residing in southwestern region of Chicago had more than five times the odds of having a PMFQR infection compared to those who did not live in this region (OR 5.26; 95% CI 1.8, 15.2; p=0.002). In contrast, a negative association was found for those children who resided in the downtown region, where there was a 97% decrease in the odds of PMFQR infection in those living in this region compared to those who did not (OR 0.03; 95% CI .002, 0.30; p=0.004).

TABLE V

MULTIVARIABLE ANALYSIS OF FACTORS ASSOCIATED WITH PMFQR
ENTEROBACTERIACEAE INFECTIONS IN CHILDREN

Associated Factor with PMFQR infection[a]	OR	95% CI	p value
Outpatient Clinic Location at time of infection diagnosis	33.1	7.06, 154.7	<0.001
Race not white, black or Hispanic	6.5	1.90, 22.2	0.003
Southwest Region (SW Chicago and SW Suburbs	5.3	1.83, 15.2	0.002
Downtown Region (Near North Side, Loop, Northside)	0.03	0.002, 0.30	0.004

[a] Abbreviations, SW, Southwest; Loop, Chicago Loop.

IV. DISCUSSION

Multi-drug resistant Enterobacteriaceae are of a growing concern globally. Much of the propagation and spread of these organisms has been related to the ST131 *E. coli* strains, high risk clones containing IncFII plasmids and other genetic structures such as transposons, integrons, and insertion sequences associated with antibiotic resistance gene cassettes yielding resistance to multiple classes of antibiotics (36). However, the transmission of beta-lactamases and other antibiotic resistance genes involves a hierarchical complex, and horizontal gene transfer involving multiple genetic elements and circulating clonal complexes are both contributing to the current pandemic of antibiotic-resistant gram-negative bacteria (37).

We also found this phenomenon occurring in our population of children. There is clear evidence of predominance of ST131 *E. coli* harboring *bla*$_{CTX-M}$. However, there is also evidence of a divergent epidemiology than adults; novel strain types are being introduced, and there is a diversity of circulating plasmid types and *bla* types, indicative of significant horizontal gene transfer between genera.

This is very worrisome from a public health perspective. Surveillance, as well as the development of effective strategies controlling spread of these organisms in children will be a unique challenge; novel strain types harboring the most threatening genes, such as carbapenemases, portends a rather complex molecular epidemiology. Additionally, other studies have shown that children, once colonized with MDR Enterobacteriaceae can remain colonized for months to years, suggesting children could serve as reservoirs and "silent disseminators" of these dangerous pathogens (38).

We posited based on the differences we found in strain types circulating in children compared to adults (in a region where such infections are endemic) that the epidemiology involving the acquisition of drug resistant bacteria in children differs. In adults cared for in the Chicago metropolitan area, MDR Enterobacteriaceae acquisition has been significantly linked to residence in long-term care facilities and with interfacility transfer, which differs from what known about children residing in this area (39, 40).

We attempted to study our hypothesis by asking whether there were residential differences in children infected with PMFQR containing Enterobacteriaceae (PMFQR Ent) compared to children who are infected with antibiotic sensitive strains. PMFQR Ent contain plasmid-based resistance genes to fluoroquinolones, an antibiotic uncommonly used in children. We found on multivariable analysis, that within one Chicago region, the Southwest region, there was a substantial increase in odds of PMFQR Ent infection, whereas in another region, the Downtown region, there was a significant decrease in the likelihood of PMFQR Ent infection (Table V). Our analysis was a multicentered study, and none of the three facilities (and no major medical centers for children) are located in the "high risk" Southwest region, yet all three centers diagnose and treat patients with PMFQR Ent infections from this region. In contrast, Hospital B, the largest hospital in the region specifically dedicated to the care of children, is located in the downtown region, and therefore services many children residing in that area; yet this was the area of "lowest risk" for PMFQR Ent infection. This may reflect linkage to bla_{CTX-M} harboring plasmids which are endemic in some communities, but the reservoirs are currently undefined.

Interestingly, we found that children with PMFQR Ent infection were more likely to present in the outpatient clinic setting than those with antibiotic sensitive Ent infections,

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suggestive that those with PMFQR Ent infections may have been less ill at the time of

presentation, and having onset of infection while in the community. An additional independent

association on multivariable analysis was the higher likelihood of PMFQR Ent infection in those

of race "other", i.e. non-white, non-black, and non-Hispanic. Due to the retrospective nature of

the study, we were unable to gather further data on specific race or ethnicity. We also did not

have travel related data for the majority of children, and it is well known that certain countries

are associated with higher rates of ESBL Ent acquisition, particularly in South and Southeast

Asia, and in regions with reduced sanitation (41, 42). It is also well described that there is an

increased risk of colonization of household members after return of the traveler who acquired an

ESBL Ent (43). Having comorbidities increases the risk of acquisition of these pathogens (44).

None of the children located in the "high risk" southwest region with PMFQR Ent infection were

of race "other", further indicating that the region itself was an independent factor for infection.

We did not find significant differences in comorbidities between the two groups.

Nevertheless, there could be environmental influences associated with the acquisition of plasmid

based antibiotic resistance genes which are associated with certain comorbidities in the pediatric

population (40). Community-based environmental influences would include higher exposure

risks in certain communities such as to certain foods, livestock, animals, water sources, fertilizer,

soil, and vegetation (45). For example, if there is a link to food exposures, such as restaurant

chains that cook with high saturated fats, and additionally serve food animals that are fed

antibiotics and hormones for growth effects, this exposure would increase the risk of acquisition

of antibiotic-resistant bacteria, as well as obesity (46, 47). This in turn increases the risk of other

diseases such as cardiovascular disease and diabetes (48). Some of the PMFQR genes, an

example, oqxA and oqxB are multidrug efflux pumps named for their resistance to olaquinadox, which is used as a growth promoter on pig farms (49).

There are additional known links of exposure to antibiotics early in childhood and the impact on the microbiome of the young child that are beyond the scope of this thesis. However, this relationship between antibiotic exposure and disruption of the resident bowel flora has been linked to several chronic diseases, including asthma, and chronic inflammatory diseases (50).

Moreover, studies in our region and nationally have suggested that an increased risk of exposure to antibiotics in children (51), as well as to antibiotic resistant bacteria, which may be related to socioeconomic status and race (52, 53). While we did assess race, we did not formally compare differences between socioeconomic factors in the regions, as we did not have street or neighborhood level data on infected patients. However, in a preliminary comparison of regional zip codes using Illinois census data, we did not find overall differences in the socioeconomic status of the "high risk" southwest region and neighboring regions such as the south and west regions.

We recognized that our study has limitations. This was a retrospective study designed to determine mechanisms of antibiotic resistance in Enterobacteriaceae recovered from children cared for at five centers in a single metropolitan area; this may potentially impact generalizability to other regions. Additionally, a plasmid based origin of the recovered antibiotic-resistance genes is supported by our DNA sequence analysis results; yet it is possible that some of these genes represent chromosomal resistance mechanisms. However, subsequent plasmid-replicon typing and DNA sequence analysis for a subgroup of bacteria support our findings on DNA microarray. Our sample size was relatively small, which may allow for selection bias; however, the pooling

of multicentered data from institutions of differing types serving diverse populations potentially lessens this bias. Additionally, the size of this study was similar to other pediatric studies assessing the epidemiology of pediatric MDR Enterobacteriaceae infections (38, 40, 42). The smaller sample sizes in pediatric studies are related to the overall low prevalence of these organisms in children in most U.S. areas (1-3%), including in the Chicago and the Midwest region (40, 54, 55). We therefore chose a case-control study design for these reasons. It should be however pointed out that national trends indicate an increase in prevalence in these menacing organisms in pediatric populations over the last decade, suggesting they are an emerging threat that needs further evaluation (14, 55-57).

In conclusion, we found that there is significant complexity and diversity in the determinants associated with beta-lactam and fluoroquinolone antibiotic resistance in children, and that pediatric MDR Enterobacteriaceae exhibited differences when compared to strains circulating in adult patients in a region where such infections are endemic. We also describe, for the first time, the impact of residence on infection with MDR Enterobacteriaceae in children located in the same geographic area, however the reservoirs remain undefined. Future studies should focus on further molecular characterization of circulating strains, and the environmental influences associated with these differences in regional acquisition. There is an imminent threat of the "silent dissemination" of multi-drug resistant Enterobacteriaceae in community settings. Local, federal, and international programs dedicated to health must focus on halting the spread of these menacing pathogens in our most vulnerable population, children.

APPENDICES

APPENDIX A

TABLE VI

REGIONAL BREAKDOWN OF PATIENT RESIDENCE BY ZIPCODE

Region	Zipcodes
Region 1 (Downtown/Near North/Loop/North)	'60601','60602','60603,'60604','60605', '60606','60607','60611','60613','60614', '60618','60630','60631', '60647', '60657', '60654'
Region 2 (Northwest Side/Northwest Suburbs)	'60739','60707','60634','60641', '60639', '60013', '60014', '60056','60081','60118', '60120','60143','60156','60169','60706', '60074','60123','60140','60192'
Region 3 (Far North Side/North Suburbs)	'60645','60626','60660','60640','60625', '60630','60656','60646','60631','60022', '60031','60046','60085','60090','60002', '60025','60030','60041','60044','60062', '60085','60090', '60093','60202','60712'
Region 4 (Near West/West Side/West Suburbs)	'60608','60616','60651','60739','60644', '60624', '60623','60612','60622','60642', '60647','60103','60104','60148','60153', '60162','60164','60177','60178','60181','60187 ', '60302', '60304','60504','60515','60523', '60525','60526','60565', '60804', '60139', '60506','60661'
Region 5 (Southwest Side/Southwest Suburbs)	'60638','60632','60609','60629','60636' '60621','60432','60436','60441','60446', '60501','60402','60432','60433','60435'
Region 6 (Southside)	'60653','60615','60637','60639','60619'
Region 7 (Far Southside/South Suburbs)	'60655','60643','60628','60617','60633', '60827','60401','60409','60422','60449', '60478' '60401','60426','60466'
Region 8 (Other parts of Illinois/Other states)	'61108','61301','48368','46368','46307', '46385','46410','20854','42141','64055', '66221','75068','20854','61032','61802'

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Rush Institutional Review Board

FWA #: 00000482

Notification of Expedited Continuing Review Approval

The following research activity has been re-reviewed and re-approved by the Institutional Review Board (IRB) at Rush University Medical Center in accordance with the Common Rule (45CFR46, December 13, 2001) and any other governing regulations or subparts. The Institutional Review Board at Rush also confirms that the project still meets the following categories under 45CFR46.110 for expedited review and in accordance with 45CFR46.110 Category 3 - Prospective collection of biological specimens for research purposes by noninvasive means & 45CFR46.110 Category 5 - Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

The following documents were reviewed and approved by the committee:

_____

Please note the date for continuing review. Although you will be notified near the time for continuing review, it is your responsibility to assure that your project receives ongoing IRB approval.

ORA Number: 10031004-IRB01-CR08
Principal Investigator: Latania Logan
Project Title: Colonization and Infection in Children with Multi-Drug Resistant Gram-Negative Bacteria: A Comparative Study of Taxonomy, Risk Factors, and Outcomes

Date of approval: 12/27/2016
Due for continuing review: 12/27/2017

Who Needs to be reconsented? No reconsent required

It is your responsibility to follow the guidelines below:

- Conduct the study in accordance with the relevant, current protocol and only make changes in the protocol after notifying the IRB, except when necessary to protect the safety, rights or welfare of subjects.
- Record and track number of subjects accrued as well as information regarding study drop-outs or withdrawals.
- Provide brief updates on the changing scientific literature as that literature pertains to the efficacy and safety of the specific procedure or intervention under study.
- Report any complaints from subjects as well as any and all serious or unexpected adverse events related to this study to the IRB.
- Maintain and use copies of the currently approved consent document related to this project (if applicable).
- Maintain a file of the consent documents bearing the signature of the subjects enrolled in this study.

{The below is a representation of an electronic record that was signed electronically and is the manifestation of the electronic signature.}
John Cobb
12/30/2016 10:40 AM
Signing for Mary Jane Welch

Mary Jane Welch, DNP, APRN, BC, CIP
Rush University Medical Center
Assoc. VP, Research Regulatory Operations
Associate Professor, College of Nursing

CITED LITERATURE

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Research Associate, Louis Stokes Cleveland Department of Veteran Affairs Medical Center, Cleveland, Ohio, 2013-

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                   Meeting, 2007

                   Thrasher Research Fund New Researcher Award (*Staphylococcus aureus*),
                   2007

                   American Lung Association (of the Upper Midwest) Senior Research
                   Training Fellowship (*Pseudomonas aeruginosa*), 2008

                   Attending of the Year, Rush University Children's Hospital, 2010

                   IDweek 2016 Investigator Award, 2016

                   Phi Kappa Phi, University of Illinois at Chicago Chapter, 2017

PROFESSIONAL
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                   Editorial Board, Pathogens and Immunity

                   Editorial Board, Journal of the Pediatric Infectious Diseases Society

SELECT
PUBLICATIONS:

ORIGINAL PEER REVIEWED RESEARCH PUBLICATIONS

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Medernach RL and Logan LK. The Growing Threat of Antibiotic Resistant Infections in Children. *Invited Article. ID Clinics N Am. In Press*.

Logan LK and Weinstein RA. The Epidemiology of Carbapenem-resistant *Enterobacteriaceae*: The impact and evolution of a global menace. *Invited Article. The*

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