Resistance in Gram-Negative Bacteria in the Pediatric Patient Population by Age and Sex

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INTRODUCTION

- Antibiotic resistant bacterial infections are associated with increased morbidity and mortality and are associated with increased cost of care[1].
- Gram-negative bacteria are more concerning due to higher virulence and the emergence of extensively drug resistant strains[2].
- Antibiotic resistance is a growing problem in the pediatric patient population. A 2013 study reported that: 25% of pediatric ambulatory care visits resulted in antibiotic prescription; 25% of children were wrongly prescribed antibiotics for viral upper respiratory infections; and 50% of all antibiotics prescriptions for children were determined to be potentially unnecessary[3].
- This extreme overuse of antibiotics in the pediatric population leads directly to increasing resistance with more exposure.
- Previous research in the adult patient population has shown an increase in antibiotic resistance in males compared to females which was evident in the 18-29 year old age group and decreased after that for decades[4]. This holds true across all common antibiotics used for serious Gram-negative infections (Fig. 2).
- Analysis of antibiotic resistance data from all positive cultures for pediatric patients over the same time period was performed to determine when this resistance pattern begins in order to begin to think about how to prevent its development.

METHODOLOGY

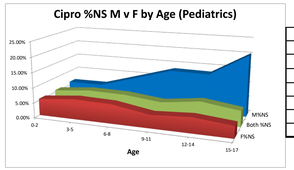
- Resistance data for all Gram-negative bacterial clinical isolates from Beaumont Health System's clinical microbiology lab between October 1st, 2010 and December 31st, 2014 was analyzed.
- The pediatric isolates were categorized into sextiles (0-2, 3-5, 6-8, 9-11, 12-14, 15-17) and the sensitivities for each antibiotic were compared based on gender and age and separated by urine isolates vs. non-urine isolates to account for potential bias based on abundance of urine samples in females.
- Duplicate samples, defined as repeat cultures from the same patient that showed the same organism and resistance pattern, were removed.

Table 1: Pediatric Patient Demographics by sex and age

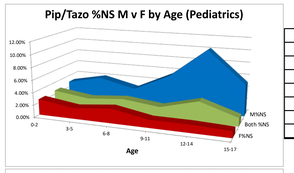
All (n=7782)						
Age (years)	0-2	3-5	6-8	9-11	12-14	15-17
N=	1786	1703	1258	869	608	1558
Female (n=6888)						
Age (years)	0-2	3-5	6-8	9-11	12-14	15-17
N=	1409	1603	1186	779	471	1440
Male (n=890)						
Age (years)	0-2	3-5	6-8	9-11	12-14	15-17
N=	376	97	72	90	137	118

Table 2: Adult Patient Demographics

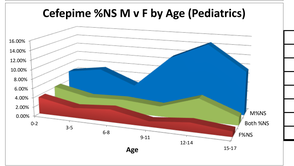
Total Population	119,102
Female	89970
Male	29,123



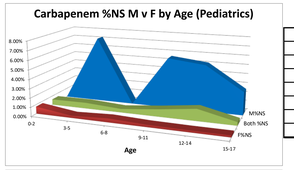
Ciprofloxacin Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	5.66%	6.12%	5.54%
3-5 Years Old	6.81%	6.19%	6.74%
6-8 Years Old	6.60%	9.72%	6.41%
9-11 Years Old	5.29%	13.33%	4.36%
12-14 Years Old	6.91%	13.14%	5.10%
15-17 Years Old	5.20%	20.34%	3.96%



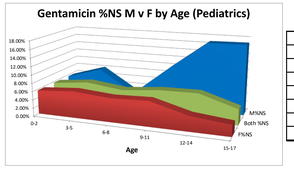
Piperacillin-Tazobactam Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	2.63%	2.93%	2.56%
3-5 Years Old	1.88%	4.12%	1.75%
6-8 Years Old	2.38%	2.78%	2.36%
9-11 Years Old	1.73%	5.56%	1.28%
12-14 Years Old	3.29%	10.22%	1.27%
15-17 Years Old	1.35%	5.08%	1.04%



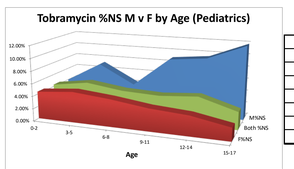
Cefepime Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	4.14%	6.12%	3.62%
3-5 Years Old	2.52%	7.22%	2.12%
6-8 Years Old	2.78%	4.17%	2.70%
9-11 Years Old	2.19%	11.11%	1.16%
12-14 Years Old	4.77%	14.60%	1.91%
15-17 Years Old	1.73%	9.32%	1.11%



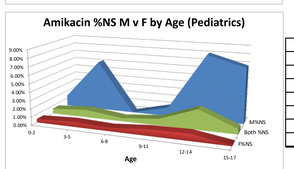
Carbapenem Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	0.62%	0.00%	0.78%
3-5 Years Old	0.65%	7.22%	0.25%
6-8 Years Old	0.40%	0.00%	0.42%
9-11 Years Old	0.81%	5.56%	0.26%
12-14 Years Old	1.32%	5.11%	0.21%
15-17 Years Old	0.39%	2.54%	0.21%



Gentamicin Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	5.71%	5.59%	5.75%
3-5 Years Old	6.64%	8.25%	6.43%
6-8 Years Old	5.56%	2.78%	5.73%
9-11 Years Old	6.44%	10.00%	6.03%
12-14 Years Old	6.58%	16.79%	3.61%
15-17 Years Old	3.79%	16.95%	2.71%

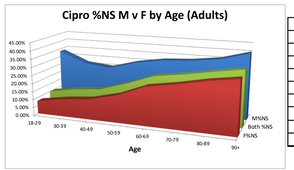


Tobramycin Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	4.31%	3.99%	4.40%
3-5 Years Old	5.17%	7.22%	4.93%
6-8 Years Old	4.37%	4.17%	4.38%
9-11 Years Old	4.14%	8.89%	3.59%
12-14 Years Old	4.61%	9.49%	3.18%
15-17 Years Old	2.82%	11.86%	2.08%

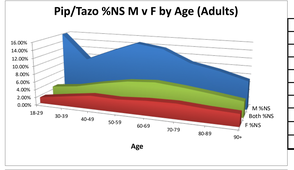


Amikacin Non-Sensitivity by Age and Sex (Pediatrics)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
0-2 Years Old	0.62%	1.33%	0.43%
3-5 Years Old	0.94%	6.19%	0.62%
6-8 Years Old	0.40%	0.00%	0.42%
9-11 Years Old	0.81%	1.11%	0.77%
12-14 Years Old	2.47%	8.03%	0.85%
15-17 Years Old	0.64%	6.78%	0.14%

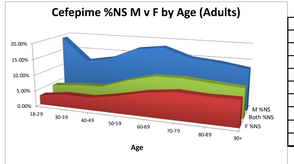
Figure 1: Percent of non-sensitive **pediatric** isolates by age group and gender for: ciprofloxacin (cipro), piperacillin/tazobactam (pip/tazo), cefepime, carbapenems, gentamicin, tobramycin, and amikacin



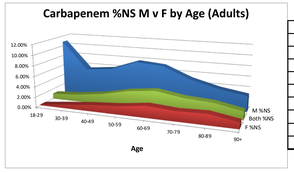
Ciprofloxacin Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	10.14%	33.58%	8.00%
30-39 Years Old	13.07%	26.87%	10.84%
40-49 Years Old	14.72%	25.19%	12.58%
50-59 Years Old	20.01%	29.72%	16.78%
60-69 Years Old	26.11%	32.49%	23.54%
70-79 Years Old	28.52%	33.50%	26.37%
80-89-Years Old	31.57%	35.77%	29.91%
90+ Years old	34.30%	40.45%	32.52%



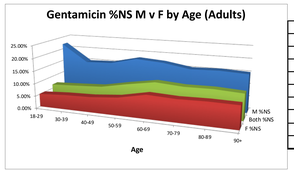
Piperacillin-Tazobactam Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	2.73%	15.92%	1.53%
30-39 Years Old	3.49%	9.47%	2.52%
40-49 Years Old	4.92%	12.19%	3.44%
50-59 Years Old	6.10%	14.65%	3.26%
60-69 Years Old	6.54%	13.61%	3.69%
70-79 Years Old	5.85%	10.53%	3.83%
80-89-Years Old	4.97%	9.12%	3.33%
90+ Years old	3.96%	7.17%	3.03%



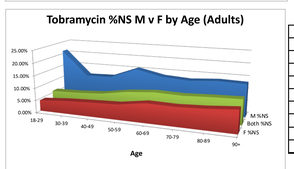
Cefepime Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	4.33%	19.03%	2.99%
30-39 Years Old	5.18%	11.75%	4.12%
40-49 Years Old	5.54%	13.25%	3.97%
50-59 Years Old	8.38%	16.90%	5.55%
60-69 Years Old	10.48%	18.01%	7.45%
70-79 Years Old	10.52%	15.13%	8.53%
80-89-Years Old	9.85%	14.35%	8.07%
90+ Years old	9.26%	13.00%	8.18%



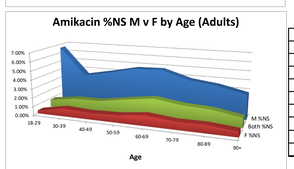
Carbapenem Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	1.04%	10.82%	0.15%
30-39 Years Old	1.39%	5.46%	0.74%
40-49 Years Old	2.03%	5.97%	1.23%
50-59 Years Old	3.14%	7.77%	1.61%
60-69 Years Old	3.74%	7.35%	2.29%
70-79 Years Old	2.90%	5.20%	1.91%
80-89-Years Old	2.58%	3.85%	2.07%
90+ Years old	1.60%	3.02%	1.19%



Gentamicin Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	6.59%	22.01%	5.19%
30-39 Years Old	7.10%	15.03%	5.82%
40-49 Years Old	7.69%	15.42%	6.11%
50-59 Years Old	9.77%	17.86%	7.08%
60-69 Years Old	11.55%	17.12%	9.31%
70-79 Years Old	10.81%	15.36%	8.85%
80-89-Years Old	10.98%	15.70%	9.11%
90+ Years old	10.38%	15.21%	8.97%



Tobramycin Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	5.77%	21.14%	4.37%
30-39 Years Old	6.05%	11.20%	5.21%
40-49 Years Old	6.69%	11.50%	5.71%
50-59 Years Old	8.47%	15.59%	6.11%
60-69 Years Old	9.35%	13.29%	7.77%
70-79 Years Old	9.09%	12.64%	7.55%
80-89-Years Old	9.60%	13.44%	8.08%
90+ Years old	9.95%	13.16%	9.02%



Amikacin Non-Sensitivity by Age and Sex (Adults)			
Age Group	All Isolates	Isolates - Males	Isolates - Females
18-29 Years Old	0.85%	6.59%	0.33%
30-39 Years Old	1.25%	3.46%	0.90%
40-49 Years Old	1.31%	4.04%	0.75%
50-59 Years Old	1.79%	4.69%	0.83%
60-69 Years Old	2.21%	4.79%	1.18%
70-79 Years Old	1.78%	3.87%	0.88%
80-89-Years Old	1.62%	3.49%	0.89%
90+ Years old	1.10%	2.80%	0.61%

Figure 2: Percent of non-sensitive **adult** isolates by age group and gender for: ciprofloxacin (cipro), piperacillin/tazobactam (pip/tazo), cefepime, carbapenems, gentamicin, tobramycin, and amikacin

RESULTS

- There were 7878 pediatric Gram-negative bacterial isolates in the database, and 96 duplicate samples were removed, leaving 7782 isolates to be analyzed.
- Cultures were much less frequent in the pediatric population than in the adult population.
- Cultures in the pediatric population were more common in the first 2 sextiles and the last sextile (Table 1)
- There were more isolates from females (n=6888) than from males (n=890) due to the preponderance of urine cultures in females.
- Antibiotic resistance generally began to rise in males during the 6-8 sextile and remained elevated over the resistance level seen in females throughout the pediatric years and into the adult years (Figures 1 and 2)
- In males, antibiotic resistance was highest for all antibiotics examined in the 12-14 and 15-17 years old sextiles.
- When analyzing the cultures based on sample type, the peak in resistance in males is seen in urine isolates, but the patterns of resistance are chaotic in non-urine isolates. This is likely attributable to the low number of non-urine isolates (Data not shown).

DISCUSSION

- Males exhibit higher levels of antibiotic resistance in the pediatric patient population which starts around the age of 9 and continues into adulthood.
- This increase in resistance by age would be obscured if not also analyzed by sex due to the preponderance of cultures from females.
- The underlying cause of this discrepancy is unclear, but it likely has to do with varying patterns of antibiotic usage.
- This is somewhat counter-intuitive as it would be expected that females have a higher overall antibiotic exposure due to the more frequent urinary tract infections.
- Actual antibiotic use data was not available for most patients as a large number of the patients were outpatient and thus the record of what antibiotics were given for a positive culture were not available.
- The peak in antibiotic resistance initially noted in 18-29-year-old males in previous research[4] is clearly shown to originate in the pediatric age group and appears to develop between the 9-11 and the 12-14 years old sextiles.
- It is clear from this data that antibiotic resistance is a greater concern in pediatrics as male children grown older but is not the same concern in female children.
- Further research is needed to determine the cause of the observed gender bias, to ascertain if it is modifiable in order to reduce antibiotic resistance.

ACKNOWLEDGEMENTS

We would like to thank the previous Oakland University William Beaumont School of Medicine medical students who have worked on the project that was the basis for this research. They include; Nichole McCaffrey, Eric Sweet, Alan Wang, Meaghan Berns, Bryan Goldman, and Lisa Spencer. Specifically the adult data shown in figure 2 was previously presented in reference #4.

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