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Use of Antibiotics in Paediatric Long Term Care Facilities

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STRUCTURED SUMMARY

Background—Adult long term care (LTC) have high rates of antibiotic use, raising concerns about antimicrobial resistance. Few studies have examined antibiotic use in paediatric LTC.

Aim—We sought to describe antibiotic use in three paediatric LTC facilities and to describe the factors associated with use.

Methods—A retrospective cohort study was conducted September 2012 – December 2015 in three paediatric LTC facilities. Medical records were reviewed for demographics, healthcare-associated infections (HAI), antimicrobial use, and diagnostic testing. Logistic regression was used to identify predictors for antibiotic use. The association between susceptibility testing results and appropriate antibiotic coverage was determined using Chi square.

Findings—Fifty-eight percent (413/717) of residents had at least one HAI, 79% (325/413) of whom were treated with at least one antibiotic course, totalling 2.75 antibiotic courses per 1000 resident-days. Length of enrolment greater than one year, having a neurologic disorder, having a tracheostomy, and being hospitalised at least once during the study were significantly associated with receiving antibiotics when controlling for facility (all $p < 0.001$). Diagnostic testing was performed for 40% of antibiotic-treated HAI. Eighty-six percent of antibiotic courses for identified bacterial pathogens ($n=201/233$) provided appropriate coverage. Having access to susceptibility testing was not associated with appropriate antibiotic choice. ($p=0.26$).

Conclusion—Use of antibiotics in paediatric LTC facilities is widespread. There is further need to assess antibiotic use in paediatric LTC. Evaluation of the adverse outcomes associated with inappropriate antibiotic use including the prevalence of resistant organisms in paediatric LTC facilities is critical.

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Keywords

paediatric; antibiotic stewardship; long term care

INTRODUCTION

Infections in children aged 0–21 years who reside in long term care (LTC) facilities are common due to underlying complex medical conditions, use of invasive devices such as urinary catheters and ventilators, and increased exposure to healthcare personnel because of enhanced care needs and developmentally appropriate therapeutic activities [1]. According to the United States Centers for Disease Control and Prevention, healthcare-associated infections (HAI) are localized or systemic responses to infectious agents that were not present nor incubating prior to healthcare facility admission [2]. Average rates of HAIs in the paediatric population, i.e., the number of incident HAIs occurring over a denominator in which each resident contributes one for each day they are observed, are 4.4 per 1000 resident-days and include acute respiratory infections, otitis media, conjunctivitis, urinary tract infections, and skin and soft tissue infections [3]. In adult LTC, HAIs due to urinary tract infections, acute respiratory tract infections and skin infections were more prevalent and accounted for the majority of antibiotic prescriptions [4].

Antibiotic use in adult LTC has been well documented, with studies showing that 47–79% of residents receive at least one course of antibiotics per year [4]. Other studies estimate the rate of antibiotic use as 0.4–23.5 courses per 1000 resident-days [5]. When used appropriately, antibiotics are an essential component of therapeutic medicine in this population [6]. However, misuse of antibiotics, including the treatment of non-bacterial infections, unnecessary application of broad spectrum agents, inappropriate course lengths and ineffective antimicrobial coverage, exposes pathogens to unnecessary antibiotic agents, which contributes to the development of antibiotic resistant strains [6]. In light of this, healthcare facilities face new incentives to implement antimicrobial stewardship programs that include on-going evaluation of prescribing practices, expert advising, intervention for inappropriate use, and prescriber education. With escalating concerns about antimicrobial resistance and increased need for antimicrobial stewardship, efforts to characterise antimicrobial use in a variety of healthcare settings are critically needed. Currently, there are almost no data on the use of antimicrobials in the growing population of children with complex medical conditions (e.g., genetic, neurologic and metabolic disorders) who reside in LTC facilities and frequently interface with acute care settings. Therefore, the aim of this study was to describe the use of antibiotics in three paediatric LTC facilities and to describe the factors associated with use.

METHODS**Study sites and population**

We conducted a retrospective cohort study as part of a quasi-experimental hand hygiene improvement trial (Keep It Clean for Kids, R01HS021470) in children residing at three paediatric LTC facilities in the New York metropolitan area [7]. The study sites and data

collection periods included a 54-bed (September 2012 through December 2015), a 137-bed (October 2012 through December 2015), and a 97-bed (November 2012 through December 2015) facility. All children < 21 years who resided in the facilities at study commencement or were admitted during the study period were included, except those admitted only for respite care. Length of stay at the study facilities ranged from one day to 21 years. The median age at study enrolment was 2.6 (inter quartile range 0.4–9.1). Prescribers at the study sites included medical doctors and nurse practitioners. During the study, prescribing support for providers included on- and off-site pharmacy, paediatric infectious disease specialist, and antimicrobial prescribing guidelines which were developed by antimicrobial stewardship teams. Detailed information on the study facilities and residents have been published previously [8]. The study was approved by either the individual site or Columbia University Medical Center institutional review board and a waiver of informed consent was granted for the study.

Data collection

A trained clinical research coordinator reviewed the medical records of all residents at time of enrolment and weekly thereafter until discharge or end of the study, whichever came first. Data collected included demographic characteristics (date of birth, sex, race, date of admission, indwelling device use including urinary catheters, central venous catheters, and tracheostomies, and chronic comorbid conditions), clinician diagnosis of HAIs (respiratory tract, gastrointestinal, bloodstream, otitis media, conjunctivitis, skin and soft tissue infection), antimicrobial prescriptions (indication, drug, duration), and associated diagnostic testing (bacterial and viral culture, direct fluorescence assay, reverse-transcriptase polymerase chain reaction testing for respiratory pathogens). Diagnostic testing was performed at both commercial and academic medical centre laboratories, which follow the Clinical Laboratory Standards Institute for the identification of organisms and their susceptibilities, when appropriate [9]. Only infections diagnosed and antimicrobial courses initiated at the paediatric LTC facilities were included in the analysis. The use of antibiotic prophylaxis for each resident was recorded as either received at least once throughout the study period or not received. Indications for prophylaxis included asplenia, perioperative, subacute bacterial endocarditis, urinary tract infection, and respiratory infection. Antibiotics initiated for non-infectious indications, e.g., “secretion management,” were not included.

Definitions

Length of enrolment was defined as the number of days from enrolment until discharge or the end of the study period, whichever came first. For residents who were discharged and readmitted, the length of enrolment only included days on which the residents were in the LTC facilities.

HAIs were defined as clinician-based diagnoses, which are guided by the McGeer criteria. For the purpose of this study, each individual antibiotic prescribed for an infection was considered an antibiotic course, e.g., if both amoxicillin and ciprofloxacin were ordered for an infection this would be considered two courses. Antibiotics that were administered orally, intravenously, intramuscularly, or aerosolised were included; topical agents as well as, antifungal and antiviral agents were excluded. Multidrug-resistant organisms (MDROs) were

defined as resistant to three or more of the following antibiotics or antibiotic classes: penicillins and extended-spectrum penicillins, cephalosporins, aminoglycosides, macrolides, quinolones, lincosamides, carbapenems, trimethoprim/sulphamethazole, and vancomycin.

Appropriate antibiotic use was defined for each antibiotic course prescribed for the treatment of an infection. An antibiotic course was considered appropriate if each identified pathogen was covered by at least one antibiotic and each antibiotic covered at least one identified pathogen. The spectrum of activity of the antimicrobial agents and the redundancy of antibiotic coverage was not considered in defining appropriate use. For pathogens identified via diagnostic testing, antibiotic appropriateness was assessed based on the accompanying susceptibility results. If no susceptibility testing was available, antibiogram data from a local paediatric hospital were reviewed. Two members of the research team—the clinical research coordinator and a paediatric infectious disease physician—worked collaboratively to adjudicate antibiotic appropriateness.

Analysis

Descriptive statistics were used to summarise demographic characteristics, HAIs, antibiotic courses, duration of antibiotic therapy, diagnostic testing, and appropriateness of antibiotic prescribing. To identify potential predictors of antibiotic use in residents, bivariate and multivariable analyses were conducted using logistic regression. For residents who had an infection with an identified bacterial pathogen, the association between the availability of susceptibility testing and antibiotic appropriateness was determined using Chi square. A p-value of <0.05 was considered statistically significant. All statistical analyses were completed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

HAIs and antibiotic utilization

Of 717 residents enrolled in the study, 58% (413/717) had at least one HAI, of whom 79% (325/413) were treated with at least one antibiotic course. The demographic characteristics of residents who received and did not receive antibiotics are described in Table I. Length of enrolment greater than one year, having a neurologic disorder, having a tracheostomy, and being hospitalised at least once during the study were significantly associated with receiving antibiotics when controlling for facility (all $p < 0.001$).

There were 1090 antibiotics ordered for 969 infections (2.75 antibiotic courses per 1000 resident-days), accounting for a total of 8729 days of therapy. The average duration of antibiotic therapy for an HAI was 9 days (median: 10 days, range: 1–60 days). HAI indications for antibiotic orders included acute respiratory tract infection (465/969, 48%) followed by otitis media (183/969, 19%), skin/soft tissue infection (130/969, 13%), urinary tract infection (92/969, 9%), presumptive or confirmed bloodstream infection (50/969, 5%), conjunctivitis (25/969, 3%), gastrointestinal infection (21/969, 2%), and other infection (3/969, 0.3%), which included one case each of meningitis, vaginitis, and submandibular adenitis.

Ten percent (95/969) of HAIs treated with antibiotics were treated with more than one class: 86 were treated with two classes and 9 were treated with three classes. One percent (9/969) of HAIs treated with antibiotics were treated with more than one drug in the same class at the same time. The classes of antibiotics ordered for the four most commonly treated HAI are shown in the Figure. Extended spectrum penicillins were the most commonly prescribed antibiotic class (426/1090, 39%) followed by cephalosporins (215/1090, 20%) and quinolones (155/1090, 14%).

Sixty-four courses of antibiotics were ordered to treat 50 bloodstream infections and included cephalosporins (46, 72%), vancomycin (9, 14%), extended spectrum penicillins (3, 5%), quinolones (3, 5%), macrolides/lincosamides (2, 3%), and linezolid (1, 2%). Forty-four courses of aerosolised tobramycin were prescribed to treat acute respiratory infections, 25% (11/44) of which were given in combination with an oral antibiotic. Lastly, there were 16 cases of *Clostridium difficile* representing 76% of all gastrointestinal infections. The most common antibiotic treatment was metronidazole (n=11/16, 69%), followed by vancomycin (n=2/16, 13%). Three *C. difficile* infections (19%) were treated with combination therapy (one course of metronidazole and cefazolin and two courses of metronidazole and vancomycin). Average length of *C. difficile* treatment was 16.8 days (median: 10.5 days, range: 7–60 days).

Microbiology of HAIs treated with antibiotics

Diagnostic testing was performed for 40% (383/969) of HAIs treated with antibiotics. Most testing was for acute respiratory infections (211/383, 55%) followed by urinary tract infections (79/383, 21%), bloodstream infections (45/383, 12%), gastrointestinal infections (19/393, 5%), skin/soft tissue infections (17/383, 4%), and conjunctivitis (12/393, 3%). Pathogens were identified in 73% (281/383) of diagnostic specimens. Of these, 81% (229/281) had one identified pathogen, 17% (48/281) had two, and 1% (4/281) had three. A bacterial pathogen was identified in 66% (183/281), a viral pathogen was identified in 30% (84/281), viral and bacterial co-infections were identified in 4% (12/281), and infections in which both a yeast and a bacterial species were identified totalled 1% (2/281). 65 Gram-positive bacteria were identified, including *Streptococcus* species (37, 60%), *Staphylococcus* spp. (20, 31%), *Enterococcus* spp. (7, 11%), and one organism was not further identified. 168 Gram-negative bacteria were identified (Table II).

Susceptibility testing and antibiotic appropriateness

There were 233 bacterial pathogens identified among HAIs treated with antibiotics and susceptibility testing was available for 47% (109/233). Only 10 organisms (9%) were multidrug-resistant: six Gram-negative pathogens had extended-spectrum beta-lactamases and four *S. aureus* were methicillin-resistant (MRSA) including one also resistant to clindamycin. Susceptibility testing and resistance patterns for Gram-negative bacteria are described in Table II. Overall, 86% (201/233) of antibiotic courses for identified bacterial pathogens provided appropriate coverage. Appropriateness was 83% (90/109) and 90% (112/124) for antibiotics assessed using susceptibility testing versus local antibiogram data, respectively. Availability of susceptibility testing was not associated with antibiotic appropriateness (p=0.26).

DISCUSSION

Over the three-year study period, 45% of residents received at least one course of antibiotics for treatment of an HAI, a mean rate of 2.75 antibiotics per 1000 resident-days. In comparison, studies in adult LTC facilities have documented that 47–79% of residents receive at least one antibiotic course over a one-year period with a mean rate of 4–7 antibiotic courses per 1000 resident-days [4, 5]. Although the overall use of antibiotics in the paediatric LTC facilities described in this study is lower than in adult LTC, the use of antibiotics to treat HAIs is similar: 79% of residents with an HAI received a course of antibiotics in this study compared to 77–94% of residents with infections in adult LTC facilities [4, 10].

Acute respiratory, urinary, and skin/soft tissue infections are cited as the three most common indications for antibiotic use in adult LTC studies [4, 11–13]. In this study of paediatric LTC, acute respiratory infections and skin/soft tissue infections were the first and third most common reasons for initiating antibiotics, but otitis media was the second most common indication and urinary tract infections accounted for only 9% of antibiotic-treated HAIs. This finding reflects age-related differences in risk for these types of infections. The types of antibiotic agents used in this study were also similar to those seen in adult LTC where use of fluoroquinolones and cephalosporins are common [5, 11, 12]. Additionally, we did note some unique patterns of antibiotic use, such as inhaled tobramycin for 9% of treated acute respiratory tract infections.

Assessment of antibiotic appropriateness is receiving increased attention in the face of growing concerns about the emergence of MDROs as well as the rise in adverse outcomes associated with antibiotic use such as *C. difficile* infection. In this study, 15% of cultured Gram-negative organisms met our definition for MDROs (resistant to 3 classes of antibiotics), which is lower than the 21–22% of multidrug-resistant Gram-negative organisms described in an adult LTC studies [14, 15]. Only four MRSA isolates were identified, though this may underestimate the true prevalence since cultures for skin/soft tissue infections were not typically obtained. While *C. difficile* was the most commonly diagnosed gastrointestinal infection, it accounted for less than 2% of HAIs. Similar rates of *C. difficile* infection have been described in adult LTC populations [12, 16]. However, treatment of recurrent *C. difficile* infection with an oral vancomycin taper accounted for the longest antibiotic duration (60 days) in these paediatric LTC facilities.

This study had limitations. One limitation was the assessment of appropriate antibiotic use, which was based solely on identification of drug-organism mismatches and did not account for redundant therapy or assess appropriateness of spectrum (broad versus narrow), duration, or dose of therapy. We also did not consider the 1% of HAIs treated with two or more antibiotics in the same class as inappropriate. These limitations may account, in part, for the higher level of appropriateness found in this study (85%) compared to studies in adult LTC (49–79%) which used different definitions of appropriateness [13, 17–19]. In addition, 30% of antibiotic-treated HAIs for which diagnostic testing was available had only viral pathogens identified. In these cases, due to poor documentation, it was difficult to ascertain whether a concurrent or superimposed bacterial infection was suspected and thus

antimicrobials prescribed. Overall, diagnoses of HAIs were not always clearly documented. Instead, symptomatology (e.g., “increased secretions”) was sometimes recorded as an indication for antibiotics. The lack of HAI definitions for paediatric LTC likely contributes to the lack of documentation of definitive HAI diagnoses. Although definitions have been developed for adult LTC, they have not been shown to be useful in paediatric populations [3]. In our analysis we included all clinician-diagnosed and documented HAIs, which may over- or under-represent the true number of HAIs at the study facilities.

This study focused on the appropriateness of antibiotics prescribed for clinician-diagnoses infections. Other areas of antimicrobial stewardship warranting further research include time to antibiotic initiation and de-escalation, intravenous versus oral formulation, course length reduction, and antibiotics prescribed without an appropriate indication.

CONCLUSIONS

This study provides important information on HAIs and antibiotic use in a growing and previously understudied population. These data underscore the need for further studies to assess and address the appropriateness of antibiotic use in paediatric LTC, especially given the frequency of transfer between acute and LTC environments. This study also highlights the importance of developing HAI definitions and antimicrobial stewardship interventions tailored to the paediatric LTC population as a means to improve antibiotic prescribing and decrease adverse outcomes associated with inappropriate antibiotic use.

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Figure. Classes of oral antibiotics used to treat 4 most common healthcare-associated infections for which antibiotics were prescribed at three paediatric long term care facilities, September 2012 – December 2015

ARI (acute respiratory tract infections), OM (otitis media), SSTI (skin/soft tissue infection), UTI (urinary tract infection). β -lactams include penicillins, extended spectrum penicillins, and cephalosporins. Other antibiotics include linezolid (n=1), metronidazole (n=2), nitrofurantoin (n=15), and vancomycin (n=1).

Table I

Demographic characteristics for residents in three paediatric long term care facilities who received and did not receive antibiotic treatment for healthcare-associated infections, September 2012 – December 2015

	Residents who received antibiotics N=325 (%)	Residents who did not receive antibiotics N=392 (%)	P-value ^c
Facility			
Site 1	78 (24)	15 (4)	–
Site 2	129 (40)	290 (74)	<0.01
Site 3	118 (36)	87 (22)	0.58
Age at admission in years, mean (range)	6.1 (0.0 – 21.0)	4.6 (0.0 – 21.0)	<0.01
Female	169 (52)	188 (48)	0.28
Hispanic	94 (29)	116 (30)	0.84
Race			
Black	86 (26)	134 (34)	–
White	85 (26)	84 (21)	0.10
Other	154 (47)	174 (44)	0.54
Duration of enrolment in days, mean (range)	798 (6–1217)	340 (1–1217)	<0.01
> 1 year of enrolment	249 (77)	113 (29)	<0.01
<i>Chronic comorbid conditions^a</i>			
Respiratory	179 (55)	182 (46)	0.02
Neurologic	279 (86)	226 (58)	<0.01
Gastrointestinal	77 (24)	153 (39)	<0.01
Immunodeficiency	3 (1)	7 (2)	0.34
<i>Indwelling device use</i>			
Feeding tube ^b	273 (84)	251 (64)	<0.01
Tracheostomy	144 (44)	69 (18)	<0.01
Mechanical ventilation	34 (10)	14 (4)	<0.01
Vascular catheter	21 (6)	28 (7)	0.72
Hospitalised during study at least once	144 (44)	50 (13)	<0.01
Received antibiotic prophylaxis	72 (22)	36 (9)	<0.01

^aRespiratory diagnoses included chronic lung disease, bronchopulmonary dysplasia, trachea/bronch/laryngomalacia, etc. Neurologic disorders included global developmental delay, epilepsy, brain injury, cerebral palsy, brain anomaly, etc. Gastrointestinal diagnoses included feeding disorder, aphagia, gastroesophageal reflux disease, etc. Immunodeficiency diagnoses included human immunodeficiency virus, asplenia, and use of immunosuppressant therapy, e.g., chemotherapy.

^bFeeding tube included nasogastric, nasojejun, gastric, gastrojejun, and jejunal feeding tubes.

^cStatistical comparison between residents who did and did not receive antibiotics was conducted using logistic regression.

Table II

Gram negative bacterial pathogens, availability of susceptibility testing, and resistance for antibiotic-treated healthcare-associated infections at three paediatric long term care facilities, September 2012 – December 2015

Organism	Number of Positive Cultures N = 168 (%)	Susceptibility Testing Available N = 92 (% of cultures) ^a	Resistant 3 Antibiotic Classes N = 26 (% of organisms) ^b
<i>Escherichia coli</i>	49 (29)	38 (78)	16 (42)
<i>Pseudomonas</i> spp.	27 (16)	11 (41)	1 (9)
<i>Klebsiella pneumoniae</i>	19 (11)	15 (79)	6 (40)
<i>Proteus mirabilis</i>	12 (7)	9 (75)	2 (22)
<i>Serratia marcescens</i>	10 (6)	7 (70)	0 (0)
<i>Haemophilus influenza</i>	8 (5)	1 (13)	0 (0)
<i>Moraxella catarrhalis</i>	5 (3)	0 (0)	0 (0)
<i>Acinetobacter</i> spp.	4 (2)	3 (75)	0 (0)
<i>Citrobacter</i> spp.	3 (2)	3 (100)	1 (33)
<i>Enterobacter</i> spp.	3 (2)	3 (100)	0 (0)
<i>Mycoplasma pneumoniae</i>	2 (1)	0 (0)	0 (0)
<i>Providencia stuartii</i>	2 (1)	2 (100)	0 (0)
<i>Morganella morganii</i>	1 (0)	0 (0)	0 (0)
Gram negative, not further identified	5 (3)	0 (0)	0 (0)

^aPercentages are of the number of positive cultures, e.g., percent of susceptibility testing available for *E. coli* is % (38/49).

^bPercentages are of the number of organisms for which susceptibility testing was available, e.g., percent of *E. coli* for which two or more resistant antibiotic classes were identified is 12% (2/17).