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IMPACT OF INFECTIOUS DISEASES SOCIETY OF AMERICA / PEDIATRIC INFECTIOUS DISEASES SOCIETY GUIDELINES ON ANTIBIOTIC CHOICE FOR HOSPITALIZED CHILDREN WITH COMMUNITY-ACQUIRED PNEUMONIA AT MAKASSED GENERAL HOSPITAL

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ABSTRACT
Background: In 2011 the Pediatrics Infectious Disease Society and the Infectious Disease Society of America (PIDS/IDSA) issued new guidelines regarding management and treatment of community-acquired pneumonia (CAP) emphasizing the use of narrow-spectrum antibiotic therapy as an empiric treatment for hospitalized children with CAP. Objectives: We assessed the impact of the 2011 PIDS/IDSA guidelines on antibiotic prescription for children hospitalized with community-acquired pneumonia at Makassed General Hospital (MGH). Methods: This retrospective chart review study included children 3 months to 18 years of age, hospitalized with clinical and radiographic evidence of CAP from December 1, 2005, through November 30, 2017, at Makassed General Hospital, Beirut, Lebanon, which is a tertiary care center. The study period was divided into pre-implementation and post-implementation periods, each over 6 years interval. We compared the impact of the 2011 PIDS/IDSA guidelines on antibiotic prescription for children hospitalized with CAP at MGH. Results: Overall, 1449 children were included. In the pre-implementation period, 905 patients were discharged from MGH with a diagnosis of CAP, with a significant decrease to 544 patients in the post-implementation period. During the pre-implementation period, 22.4% of children with CAP received third-generation cephalosporins, whereas this percentage decreased to 13.6% in the post-implementation period ($p < 0.0001$). However, the percentage of children who received amoxicillin-clavulanic acid in the pre-implementation period was 53.5% and increased to 66.2% in the post-implementation period ($p < 0.0001$). Macrolide monotherapy was common in both, pre-implementation (30.1%) and post-implementation (39%) guideline periods ($P < 0.0001$). Concurrent use of macrolide with amoxicillin-clavulanic acid increased significantly to 24.2% ($p < 0.0001$). Conclusion: After implementation of guidelines, third-generation cephalosporin use declined and penicillin/ampicillin/amoxicillin-clavulanic acid use increased among children hospitalized with CAP.

KEYWORDS: Community-acquired pneumonia, antibiotics, antibiotics stewardship, antimicrobial, pediatrics, hospitalization, guidelines, prescription.

INTRODUCTION
Pneumonia is the single greatest cause of death in children worldwide.[1] Each year, more than 2 million children younger than 5 years die of pneumonia, representing ~ 20% of all deaths in children within this age group.[2]

In August 2011, the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) published an evidence-based guideline for the management of CAP in children. These guidelines recommended specific measures to standardize the evaluation and treatment of CAP in children.

Despite these guidelines, there is significant variability in antibiotic prescribing practices in pediatric primary care settings[3], including both the choice to use antibiotics at all and, if antibiotics are chosen, the specific agent selected.[4,5]

Because Streptococcus pneumoniae is the most common bacterial cause of pediatric CAP and narrow-spectrum β-lactam antibiotics effectively target S. pneumoniae, these guidelines recommended that fully immunized children without underlying complications who require hospitalization receive an aminopenicillin as first-line antibiotic therapy.[6]

Prior to the publication of the guidelines, <10% of hospitalized children with CAP received penicillin or ampicillin/amoxicillin; most children received cephalosporins and prescribing varied significantly across physicians and institutions.[7,8]

Additionally, the guideline recommends empirical combination therapy with a macrolide and β-lactam antibiotic when atypical pneumonia is a diagnostic consideration.

Furthermore, broad-spectrum antibiotics, such as cephalosporins, have no advantage over amoxicillin for treatment of S.pneumoniae and put children at risk for adverse events, while contributing to the global problem of antibiotic resistance.[9]

Antibiotic stewardship programs and management guidelines have been shown to improve the selection of appropriate investigations and antibiotics for management of infections in children.[10] Use of appropriate antibiotics would allow the opportunity to save healthcare resources and reduction of antibiotic drug resistance which are becoming global challenges.[11,12]

Our main outcome is to assess the impact of the 2011 PIDS/IDSA guidelines on antibiotic prescribing for children hospitalized with community-acquired pneumonia at MGH, and hospital-level implementation efforts were determined by assessing the yearly percentage of children receiving third-generation cephalosporin or penicillin/ampicillin.

METHODS

Study design: This was a retrospective chart review of hospitalized children treated for community-acquired pneumonia, admitted to Pediatrics Department at Makassed General Hospital, Beirut, Lebanon, a tertiary center. It was conducted between December 1, 2005, and November 30, 2017, and divided into pre-implementation and post-implementation periods, each done over 6 years interval. In this pre-implementation and post-implementation study that included 905 and 544 patients respectively, researchers compared the impact of the 2011 PIDS/IDSA guidelines on antibiotic prescribing for children hospitalized with CAP at MGH.

Inclusion/Exclusion criteria: Researchers included all pediatric patients, between 3 months and 18 years, admitted to Pediatrics Department at MGH between December 2005 and November 2017 with an ICD-10 diagnosis of Pneumonia, receiving antibiotics within the first 48 hours of admission, with no prior hospitalization within one month, and not known to have Cystic Fibrosis, Immunodeficiency or Tracheostomy.

Methodology: After obtaining the approval from the Institutional Review Board (IRB) of MGH, data collection started. Hospital administrative records were reviewed to identify all children with an International Classification of Diseases, tenth revision (ICD-10) billing code, consistent with pneumonia. Specific inclusionary ICD-10 codes were: J13, J15.0, J15.1, J15.3, J15.7, J15.9, J18, J18.0, J18.1, J18.9.

The study was divided into pre-implementation (December 1, 2005, till August 31, 2011) and post-implementation (October 1, 2011, till November 30, 2017) periods.

September 2011 was considered a transition period, during which the 2011 PIDS/IDSA guidelines for management and treatment of community-acquired pneumonia were presented at departmental grand rounds as part of a lecture on the importance of adherence to guidelines regarding antimicrobial use, and on yearly basis was reviewed and presented to all residents as part of the yearly curriculum.

A data collection sheet was developed, based on the outcomes of this study and the published PIDS/IDSA guidelines regarding the antibiotic choice for treating community-acquired pneumonia. The data collection sheet covered the following main sections: Demographic data, Associated co-morbidities, Immunization status, Clinical assessment, Diagnostic criteria, Antibiotic use, Clinical assessment after 48 hours.

Statistical analysis: The Statistical Package for Social Sciences (SPSS, version 24) program was used for data entry, management, and analysis.

Categorical variables were presented as number and percent, whereas continuous variables were presented as mean and standard deviation. Bivariate analysis was carried out by using the chi-square for comparing categorical variables, whereas continuous ones were compared using the Student's t-test. A multivariate analysis was conducted to control for confounding variables. A p-Value of ≤ 0.05 was used to indicate statistical significance.

RESULTS

There were 1449 patients who were discharged with a diagnosis of pneumonia and met the eligibility criteria during the study period. Of these, 905 patients were discharged between December 1, 2005, and August 30, 2011, and 544 patients were discharged between October 1, 2011, and November 30, 2017.

The baseline characteristics of enrolled children were similar in the pre-implementation & post-implementation groups and showed no difference in age and gender. Mean age was 3 years; 56% were male. (Table 1).

The percentage of associated co-morbidities was found in 43% of children, with asthma being the most common co-morbidity in both groups. An increase in the percentage of asthmatic and premature patients was

noted in the post-implementation period to 27.6% (p = 0.01) and 7% (p=0.03) respectively. (Table 2).

Concerning the immunization status, we noticed a significant increase in the immunization of Pneumococcal & Influenza in the post-implementation period, to 22.4% (p<0.0001) and 4.4% (p<0.0001) respectively. Hib & Pertussis are already given in all dispensaries because it is provided by the Ministry of Health (MOH) & this study showed that they were given in around 80% of patients in both periods.

Blood cultures were obtained in 76% in the pre-implementation period with a significant increase to 90.1% in the post-implementation period (p<0.0001).

Of those, 11 (0.9%) blood cultures were considered true positive, S.pneumoniae was found in 7, Klebsiella ESBL in 2, Enterobacter in 1, and S. aureus in 1. The other positive blood cultures were considered a contaminant (1.7%). (Table 3).

DTA cultures were performed in 81 patients (9%) in the pre-implementation period, while this decreased in the post-implementation period to 21 (3.9%) with a statistically significant p-value of < 0.0001. (Table 3)

Chest X-ray was done in almost all children hospitalized for CAP (98.7% and 99.3%). (Table 3)

In the post-implementation period, testing for respiratory viruses was performed. RSV in 26.8% (p<0.0001), Influenza 7.5% (p<0.0001), and Adenovirus 2.2% (p<0.0001). (Table 3).

While testing for atypical bacteria, mainly Mycoplasma Pneumonia was performed almost the same in both groups, 46.3% and 48.5% (p=0.41). But the positive values of mycoplasma pneumonia were more in the post-implementation period (p=0.006). (Table 3).

Penicillin/Ampicillin were noted 0.4% in the pre-implementation, with 1.1% in the post-implementation period, with a p-value of 0.19.

In the pre-guideline period, third-generation cephalosporins were prescribed in 22.4%, however, Amoxicillin-Clavulanic acid was common in 53.5% of admitted children with CAP. In the post-implementation period, the percentage of children who received empirical treatment with third-generation cephalosporins progressively declined to 13.6%, whereas amoxicillin-clavulanic acid increased to 66.2%, with both being statistically significant (Table 4).

The study showed a yearly increase in the use of Amoxicillin-Clavulanic Acid in the post-implementation period, as opposed to Third-Generation Cephalosporins which showed a significant yearly decrease in its use in the post-implementation period, with both antibiotics compared to their pre-implementation projection (Figure 1).

The concurrent use of macrolide with amoxicillin-clavulanic acid and third-generation cephalosporins increased in the post-guideline period. Macrolide monotherapy increase in the post-implementation period with p-value <0.0001.

Vancomycin was the same in both groups, pre-implementation (1%) and post-implementation (1.6%) with a p-value of 0.27.

Second-generation Cephalosporins were not used anymore in the post-implementation period (0%), with a p-value <0.0001.

We further studied if the patients were started on an antibiotic during this illness prior to their admission. In the pre-implementation period, 25.1% received antibiotics, and 27% in the post-implementation (p=0.41). The mean days of antibiotics received prior to admission in both groups was 4 and 3.5 days (p=0.05). Further studying the type of antibiotics used, showed a significant increase in the use of Third-generation cephalosporins from 19.4% to 39.5%, with no increase in the use of amoxicillin-clavulanic acid or Penicillin/Ampicillin (Table 5).

The follow-up studies after ≥ 48 hours of admission showed a significant decrease in repeating Chest X-ray 19.8% to 14.9% (p=0.02). however, laboratory studies were repeated almost the same in both groups 21.4% and 21.3% (p=0.96), cultures were repeated in 3.1% and 3.5% (p=0.68). (Table 6).

Upon studying the outcomes, this study showed that patients who required ICU admission were almost the same, 38 (4.2%) and 32 (5.9%) with a p-value of 0.15. Complications were noted in 26 (2.9%) in the pre-implementation and 19 (3.5%) in the post-implementation period (p=0.51). One patient had osteomyelitis in the pre-implementation period, while all other noted complications in both groups were related to pleural effusion. Mortality rates were not noted in the post-implementation period (p=0.51). (Table 7).

Table. 1: Demographic characteristics of children hospitalized with CAP in the pre-Implementation and post-Implementation periods.

Characteristics	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Age (years)	2.9 (2.9)	3.1 (2.8)	0.31
Gender			
Male	506 (55.9%)	303 (55.7%)	0.94
Female	399 (44.1%)	241 (44.3%)	

Table. 2: The associated comorbidities of children hospitalized with CAP in the pre-Implementation and post-Implementation periods.

Associated Comorbidities	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Asthma	196 (21.7%)	150 (27.6%)	0.01
Prematurity	39 (4.3%)	38 (7.0%)	0.03
Congenital Heart Disease	27 (3.0%)	24 (4.4%)	0.15
Seizure	31 (3.4%)	18 (3.3%)	0.91

Table. 3: The diagnostic criteria (bacterial, radiological, viral, atypical) performed for children hospitalized with CAP in the pre-Implementation and post-Implementation periods.

Diagnostic Criteria	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Blood culture	688 (76.0%)	490 (90.1%)	<0.0001
DTA culture	81 (9.0%)	21 (3.9%)	<0.0001
Chest X-ray	893 (98.7%)	540 (99.3%)	0.29
RSV nasal wash	0 (0%)	146 (26.8%)	<0.0001
Influenza nasal wash	2 (0.2%)	41 (7.5%)	<0.0001
Adenovirus in stool	0 (0%)	12 (2.2%)	<0.0001
Mycoplasma Pneumoniae IgM	419 (46.3%)	264 (48.5%)	0.41

Table. 4: The type of antibiotic used upon admission for children hospitalized with CAP in the pre-Implementation and post-Implementation periods after ≥ 48 hours of admission

Type of antibiotics	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Amoxicillin-Clavulanic Acid	484 (53.5%)	360 (66.2%)	<0.0001
With Macrolide	52 (10.7%)	87 (24.2%)	<0.0001
Third Generation Cephalosporins	203 (22.4%)	74 (13.6%)	<0.0001
With Macrolide	49 (24.1%)	22 (29.7%)	0.35

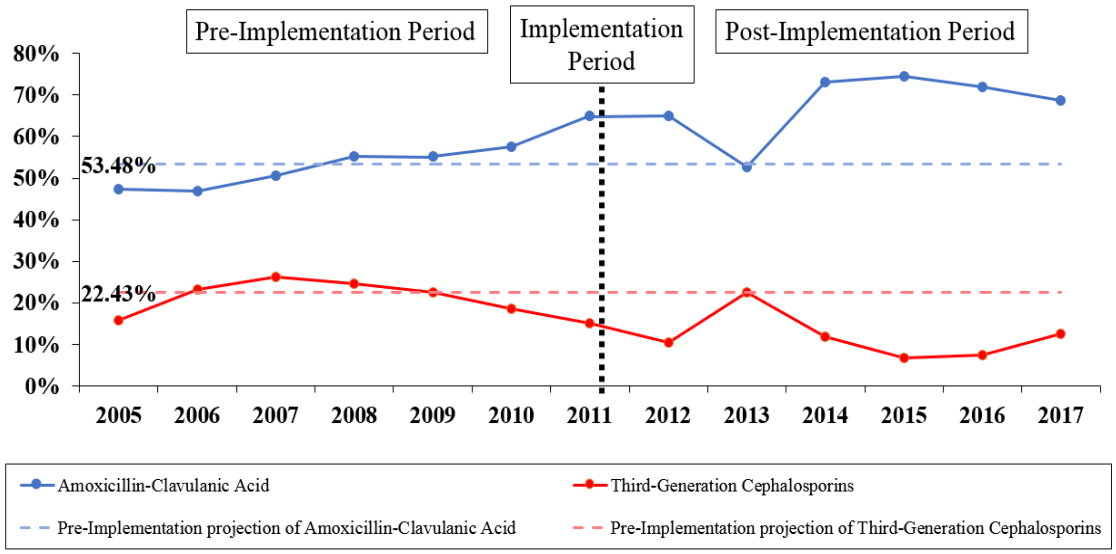

Figure. 1: The yearly use of Amoxicillin-Clavulanic Acid as compared with the yearly use of Third-Generation Cephalosporins, with each of them compared to its pre-implementation projection.

Table. 5: The type of antibiotic used prior to admission of children with CAP in the pre-Implementation and post-Implementation periods after ≥ 48 hours of admission

	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Use of antibiotic			
No	678 (74.9%)	397 (73.0%)	0.41
Yes	227 (25.1%)	147 (27.0%)	
Type of antibiotic			
Ampicillin/Penicillin	4 (1.8%)	1 (0.7%)	
Amoxicillin-Clavulanic Acid	67 (29.5%)	43 (29.3%)	
First Generation Cephalosporins	4 (1.8%)	2 (1.4%)	
Second Generation Cephalosporins	27 (11.9%)	5 (3.4%)	
Third Generation Cephalosporins	44 (19.4%).	58 (39.5%)	<0.001
Macrolide	51 (22.5%)	34 (23.1%)	
Unknown	30 (13.2%)	4 (2.7%)	
Mean days	4.0 (2.6)	3.5 (2.5)	0.05

Table. 6: The repeated diagnostic testing performed for children hospitalized with CAP in the pre-Implementation and post-Implementation periods after ≥ 48 hours of admission

Follow-up	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Laboratory tests	194 (21.4%)	116 (21.3%)	0.96
Cultures	28 (3.1%)	19 (3.5%)	0.68
Chest X-ray	179 (19.8%)	81 (14.9%)	0.02

Table. 7: The outcome (morbidity and mortality) for children hospitalized with CAP in the pre-Implementation and post-Implementation periods after ≥ 48 hours of admission.

Outcome	Pre-Implementation (n=905)	Post-Implementation (n=544)	p-Value
Required ICU admission	38 (4.2%)	32 (5.9%)	0.15
Complications	26 (2.9%)	19 (3.5%)	0.51
Mortality	5 (0.6%)	0 (0%)	0.16

DISCUSSION

In the pre-implementation period, over 6 years, the number of discharged patients with an ICD-10 diagnosis of community-acquired pneumonia was 905, while this number decreased to 544 patients in the post-implementation period. These findings suggest that immunization, that was noted to be increased with a statistical significance, plays an important role in decreasing the number of patients admitted and thus infected with CAP. And the increase in testing for respiratory viruses (RSV, Influenza, and Adenovirus) can modify the clinical decision making a child with suspected pneumonia because antibacterial therapy was not anymore routinely required for these children in the absence of clinical or laboratory findings that suggest bacterial coinfection.[13]

Williams et al, in a prospective study nested within the Centers of Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC), showed that the 2 institutions that incorporated active, hospital-based educational efforts demonstrated the largest reductions in third-generation cephalosporin use along with the largest increase in penicillin/ampicillin use.[14] Ambroggo et al, demonstrated that the development of hospital-based practice guidelines with an educational campaign and modification of an existing CAP order set, increased guideline-concordant antibiotic prescribing for children hospitalized with CAP from 30% to 100% within 6 months.[15] Our hospital had hospital-based educational efforts, as the guidelines were presented and reviewed on yearly basis. However, neither hospital-based CAP management guideline nor existing order sets were available.

We studied the impact of PIDS/IDSA guidelines on antibiotic prescribing for children hospitalized with CAP. The use of third-generation cephalosporins declined significantly from 22.4% in the pre-implementation period to 13.6% in the post-implementation period. The use of amoxicillin-clavulanic acid increased significantly from baseline of 53.5% in the pre-implementation period to 66.2% in the post-implementation period. Therefore, these changed were consistent with the PIDS/IDSA guidelines regarding the use of penicillin/ampicillin instead of broader-spectrum third-generation cephalosporines for most children hospitalized with community-acquired pneumonia.

Awor et al, in Uganda showed the use of Amoxicillin in 91% of patients with CAP.[16] Thomson et al, in USA showed its use in 63.6%[17] and Ivanovska et al, in Netherland, showed its use in 63%.[18]

Donà et al, in a literature review, reported the association of aminopenicillins often prescribed: amoxicillin + clavulanate was found to be the most used therapy by studies conducted in Saudi Arabia[19], France[20], and India.[21]

Monotherapy use of macrolide increase in the post-implementation period. Handy et al, a retrospective cohort study in an outpatient pediatric primary care network including 10414 children, demonstrated that the majority of physicians were prescribing macrolides.[22] Although the bacterial etiology of CAP is changing with the introduction of pneumococcal vaccines, S. pneumoniae remains till now the leading cause of bacterial CAP, and guidelines recommend strongly targeting this organism.[23]

Concurrent use of macrolide increased in the post-implementation period. Although macrolides are often used for a suspected atypical CAP, several studies raised the concern regarding increase the use of macrolide and thus the development of antibiotic resistance.[24,25] Adult guidelines recommend a macrolide-cephalosporin combination therapy for CAP[26], the PIDS/IDSA guidelines do not recommend routine macrolide combination therapy for children. Thus, this increase in concurrent macrolide use is not consistent with the PIDS/IDSA guidelines. However, the PIDS/IDSA guidelines suggest consideration of macrolide combination therapy only in specific circumstances, but this recommendation was rated as weak and based on moderate-quality evidence.

The probable reasons for prescribing more macrolide in our hospital may be due to three reasons. First, this study showed a significant increase in the positive values of Mycoplasma titer to 22.6% (p-value=0.006). Second, Mycoplasma titer is performed once per week in our lab, so whenever expecting atypical pneumonia, macrolide was started. Third, the practice of individual physicians and having the macrolide being prescribed without an ID consultation.

The collection of blood cultures in patients hospitalized with CAP has traditionally been considered a marker of high-quality care and has been recommended by the American Thoracic Society since the 1990s as part of the initial evaluation of these patients.[27] However, this practice has increasingly been questioned, particularly in adult literature where studies suggest that blood culture yield is low and results rarely change management. [282930] In our study, blood culture was collected in 76% of patients in the pre-implementation and 90.1% in the post-implementation period with only 0.9% of both groups were truly positive. Tam et al, in a multicenter retrospective study, showed that blood cultures were collected in 61% of patients, with only 2% of them were positive. And noted that these results did not lead to change in management, and positivity was not associated with poor clinical outcome.[31]

Practice guidelines are intended to improve quality of care by encouraging prescribing practice that follows the best evidence available and expert consensus. [33,32]

Our study showed that there was no difference in the outcome of both groups regarding the ICU admission and complications, with a 0% of mortality in the post-implementation period. Guidelines targeting antimicrobial prescribing can be an important tool for reducing inappropriate and unnecessary antibiotic use in the effort to improve clinical outcomes while minimizing antimicrobial resistance. Guidelines for the treatment of CAP can be effective in improving quality of care. Multiple studies have shown that adherence to American Thoracic Society and Infectious Disease Society of America guidelines for treatment of CAP in adults is associated with improved clinical outcomes and reduced costs. [34,35]

Our study showed an increase in the use of third-generation cephalosporins with no increase in the use of amoxicillin-clavulanic acid when prescribed prior to the patients' admission. Reasons might include barriers awareness and/or agreement with recommendations, the inertia of previous practice,[36] and having the antibiotics in Lebanon part of over-the-counter medications.

Limitations

First, we did not analyze individual practices to ascertain awareness of the PIDS/IDSA guidelines or individual preferences for antibiotic prescription. However, we evaluated the awareness of the whole MGH institution to the national guidelines.

Second, this study is a retrospective chart review study, based on the ICD-10 codes to identify the patients with CAP which could result in misclassification. However, we reviewed all the charts and excluded those with a diagnosis other than CAP.

Third, this study is a single centered study done at Makasssed General Hospital, to assess the impact of antibiotics choice for hospitalized patients with CAP. Thus it is not a generalizable study.

CONCLUSION

After implementation of the PIDS/IDSA guidelines that recommended the use of narrow-spectrum antibiotic therapy as an empiric treatment for hospitalized children with CAP, adaptation can be noted by an increase in the use of Amoxicillin-Clavulanic acid with a decrease in the use of Cephalosporin. However, the use of both monotherapy macrolide and concurrent use of macrolide increased.

Guidelines have not yet been fully adopted, and continued efforts to educate physicians, modify clinical practice. The barriers must be addressed to ensure widespread and effective implementation of guidelines in local environments. Identify the most effective hospital-

based strategies to facilitate better implementation of the guidelines. We recommend encouragement of more vaccination, ordering more viral and atypical serologies when indicated. Performance of mycoplasma titer more than once per week in our lab. Antibiotics are not over-the-counter medications, thus should be strictly prescribed by physicians with more adherence to the IDSA/PIDS guidelines. Conduction of further prospective multicenter studies is recommended.

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