

Infections and Asthma in the Pediatric Intensive Care Unit: Prevalence and Contribution to Disease Severity

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This study was performed to ascertain the prevalence of respiratory infections in pediatric intensive care unit (PICU) asthmatics and whether infections increase morbidity. A retrospective cohort study on patients admitted to PICU for status asthmaticus over a 3 year period. Hospital course, radiographic findings, and microbiology data were reviewed. Statistical analyses were performed and covariates with $P \leq 0.05$ were considered significant. Four hundred forty-eight patients were admitted during the study period. One hundred fifty-nine infectious pathogens were identified in 146 patients. Thirty-seven percent of patients tested for viruses were positive and 11% tested for mycoplasma pneumonia had positive IgM serology. PICU length of stay (LOS) and overall LOS for patients with infection were greater than those without ($P=0.05$). Thirty-one patients required mechanical ventilation and 9 had bacterial or viral infections. There was no difference in the rate of intubation or length of ventilation for those with infection compared to those without. Eighty-three patients were discharged with diagnosis of pneumonia, but 254 received antibiotics in the PICU. Patients with fever (OR 1.9, CI 1.1, 3.0), intubated (OR 17.1, CI 4.5, 65), or a CXR read as pneumonia (OR 16, CI 6.1, 41.7) were more likely to receive antibiotics in the PICU ($P < 0.05$). Viral infections are common in PICU patients with status asthmaticus. Patients with infections have a greater LOS than those not infected, but do not have increased rate of intubation or length of ventilation. Patients receive antibiotics based on clinical and radiographic findings, but laboratory testing rarely confirms the presence of bacterial or atypical infections.

Introduction

RECENT DATA HAVE indicated that more patients are requiring admission to pediatric intensive care units (PICUs) for status asthmaticus.¹ Studies on children and adults have demonstrated that viral infections are the most common cause of acute asthma exacerbations.^{2–6} There are conflicting data in adults on what role atypical infections contribute to disease severity and when they should be treated and this is even less clear in hospitalized children.^{6–10} To better understand how infections contribute to clinical course, we retrospectively evaluated children admitted to our PICU with status asthmaticus. Our objective was to determine the prevalence of respiratory infections, how they affected the disease severity and hospital course, and whether patients were treated appropriately with antibiotics in the PICU.

Materials and Methods

Before initiating the study, approval was obtained from the Institutional Review Board and they waived the need

for informed consent. A retrospective cohort study was performed on patients admitted to a 20-bed tertiary PICU at a children's hospital during a 3-year period. The inclusion criteria were: status asthmaticus, acute asthma exacerbation, or reactive airways disease (RAD) as identified by ICD-9 codes 493.00–493.91 as primary diagnosis from a PICU database. A patient was considered to have RAD if they were between 6 months and 3 years of age, had previously been treated for wheezing, and had home medications for wheezing. Exclusion criteria were: age less than 6 months and had bronchiolitis (ICD-9 code 466.19).

Parameters reviewed and recorded included: age, sex, Pediatric Risk of Mortality (PRISM) 3 score,¹¹ symptoms, diagnoses, medications, duration of ventilation, length of stay (LOS), month of admit, and laboratory and radiographic results. Tests for infections included: nasopharyngeal viral direct fluorescent antibodies (DFA), nasal swab for viral polymerase chain reaction (PCR) and viral cultures, respiratory bacterial cultures, nasopharyngeal *Bordetella pertussis* PCR, and serum antibodies for *Mycoplasma pneumoniae*. Respiratory bacterial cultures were obtained from sputum,

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endotracheal aspirate, or bronchioalveolar lavage (BAL). During the study period, our laboratory changed from viral testing by DFA and viral culture to a PCR panel and so both modalities were used to diagnose infections.

Patients were defined as being “infected” if they had a microbiology or serology test that was positive for a pathogen. Not all “infected” patients were identified as having pneumonia. Screening tests for infection were ordered at the physician’s discretion based on clinical presentation. Patients were defined as having pneumonia if that was given as the discharge diagnosis (ICD-9 code 486) and if chart review identified fever of greater than 100.4°F and infiltrate on radiograph.

Continuous variables were compared with Student’s *t*-test for normally distributed variables or Mann–Whitney *U* test for non-normally distributed variables and categorical data were compared with Fisher’s exact test. Logistic regression multivariable analysis was also performed and covariates with $P \leq 0.05$ were considered significant. A logistic regression model was developed evaluating a potential independent association between use of antibiotics while in the PICU and the following variables: fever, age less than 2 years old, WBC >15K, concurrent use of oral steroids or antibiotics before admission, intubation, chest radiograph (CXR) read as pneumonia, and patient given antibiotics in the emergency department.

Patients were treated in accordance with our standard PICU guidelines for status asthmaticus that are incorporated in an order set. Standard therapy included glucocorticoids and continuous albuterol. Other additional therapies depended on the response to standard therapy and included Heliox, intravenous magnesium sulfate, ipratropium bromide, and aminophylline and terbutaline intravenous infusions.

Results

During the study period, 448 patients were admitted for status asthmaticus, acute asthma exacerbation, or RAD and

159 infectious pathogens were identified in 146 patients. Tests for viral infections were positive in 130 out of 352 patients, yielding a prevalence of 37% of the patients screened. More patients had a viral infection from December through February than the rest of the year (38 versus 22%, $P=0.003$). The most common viral infections were enterovirus/rhinovirus (48%), respiratory syncytial (20%), and influenza virus (20%). The most frequent bacterial infection was *M. pneumoniae*. Of the 205 patients tested, 22 patients had positive IgM antibodies (11%), 18 of which received antimicrobial therapy. When comparing the patients who tested positive and received therapy and those who did not receive therapy, there was no significant difference in LOS. Four out of 22 patients IgM positive for *Mycoplasma* were diagnosed with pneumonia, but there was no difference in frequency of pneumonia when compared to the group that was IgM negative (13 out of 183). Other bacterial pathogens included: *Staphylococcus aureus*, *Pneumococcus*, *Moraxella catarrhalis*, *Haemophilus influenza*, Group A streptococcus, and *Enterobacter cloacae* (Table 1).

Patients with laboratory documented infections experienced longer overall LOS (5.9 versus 4.9 days, $P=0.007$) and PICU LOS (2.9 versus 2.4 days, $P=0.05$) than patients without documented infection. There was no difference in the frequency of rhinorrhea or total white blood cell count, but more infected patients had fever, cough, were diagnosed with pneumonia, and received antibiotics (Table 2).

There was no difference in the PRISM 3 score or the rate of intubation for patients with infections compared to those without infections. Overall, 31 patients (7%) required invasive mechanical ventilation, 9 of whom (29%) had documented infections: 4 patients with bacterial infections and 5 patients with viral infections. A total of 4 out of 26 samples from tracheal aspirate or BAL were positive, but 3 patients’ cultures grew 2 different organisms that were not identified as normal respiratory flora. There was no difference in the length of intubation for those with infection compared to those without. Seven patients (1.5%) received noninvasive

TABLE 1. PATHOGEN IDENTIFICATION

Pathogen	DFA	PCR	Viral culture	Respiratory culture	Serology
Entero/rhino		31			
Enterovirus			24		
Rhinovirus			8		
RSV	25	1	3		
Influenza	16	1	10		
HMPV	7				
Adenovirus	3		1		
Parainfluenza	2				
HSV			1		
CMV			1		
<i>Staphylococcus aureus</i>				1	
<i>Pneumococcus</i>				2	
<i>Moraxella catarrhalis</i>				1	
<i>Haemophilus influenza</i>				1	
<i>Enterobacter cloacae</i>				1	
Group A streptococcus				1	
<i>Mycoplasma pneumonia</i>					22

A total of 259 viral DFA (direct fluorescent antibody) tests, 93 viral PCR, 26 respiratory cultures, and 205 *Mycoplasma pneumonia* IgG and IgM serologies were obtained. *Moraxella* and *Haemophilus* were obtained by BAL and *Staphylococcus*, Group A *Streptococcus*, and *Enterobacter* were obtained by endotracheal aspirate (ETT). *Pneumococcus* was obtained from BAL on one patient and ETT on another.

BAL, bronchioalveolar lavage; CMV, cytomegalovirus; DFA, direct fluorescent antibodies; HMPV, human metapneumovirus; HSV, herpes simplex virus; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

TABLE 2. PATIENT CLINICAL CHARACTERISTICS BY PATHOGEN DETECTION STATUS, *N* = 448

Parameter	Infected (<i>n</i> = 146)	Noninfected (<i>n</i> = 302)	P
Age (months)	77 ± 47	83 ± 51	0.26
Sex (male)	96 (66)	199 (66)	1
PRISM 3	3.6 ± 4.2	2.98 ± 2.9	0.19
Viral pathogens	130	0	
Bacterial Pathogens	29	0	
Fever	92 (63)	86 (28)	0.0001
Cough	140 (96)	255 (84)	0.0003
Rhinorrhea	72 (49)	140 (46)	0.61
WBC	14.8 ± 8.3	15.4 ± 5.8	0.6
Pneumonia	43 (29)	40 (13)	0.0001
PICU antibiotics	105 (72)	148 (49)	0.0001
PICU LOS (days)	2.9 ± 2.4	2.4 ± 1.4	0.05
LOS (days)	5.9 ± 4	4.9 ± 2.2	0.007
Intubated	9 (6)	22 (7)	0.8
LOV (h)	68.5 ± 78	33 ± 30	0.2

Number (percentage) or average ± standard deviation. Infected patient is defined as positive microbiology or serology test for infection and pneumonia is defined by ICD 9 code on discharge diagnosis and presence of fever of 100.4°F or greater and infiltrate on radiograph.

Bold values are statistically significant.

LOS, length of stay; LOV, length of ventilation; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality.

mechanical ventilation, 10 (2.3%) received high-flow nasal cannula and there was no difference in the use of these modalities in the patients with documented infections compared to those without. One patient died due to complications from an out-of-hospital cardiac arrest.

Eighty-three (9%) patients were appropriately discharged from the hospital with the diagnosis of pneumonia based on the criteria of fever of greater than 100.4°F and an infiltrate on CXR. However, 254 (57%) received antibiotics while in the PICU and 110 (25%) patients were discharged home on antibiotics. Patients with fever (OR 1.9, CI 1.1, 3.0), intubated (OR 17.1, CI 4.5, 65), or a CXR read as pneumonia (OR 16, CI 6.1, 41.7) were more likely to receive antibiotics in the PICU (*P* < 0.05). Patient age less than 2 years, WBC > 15K, receiving antibiotics in the emergency department (ED), and antibiotics or steroids before admission did not increase the odds of receiving antibiotics in the PICU.

Discussion

This study presents the most detailed data on infections in PICU patients with acute asthma exacerbations to date. We found they have a greater LOS in both the PICU and hospital than those without infection. Prior pediatric studies on hospitalized asthmatic patients have also noted that viral infections lead to increased LOS, duration of oxygen requirements, and need for PICU admission.^{12,13} Although the infected patients in our study had a greater LOS, we did not find greater rates of intubation, increased length of ventilation, or more frequent use of noninvasive ventilation compared to those without infection. Our overall low rate of intubation, infrequent use of noninvasive ventilation, and low mortality are also consistent with 2 recent pediatric studies on asthma.^{1,14} The mortality and PICU LOS for all patients are also consistent with what was predicted from the severity of illness or PRISM 3 score.

The most common infections in patients admitted to the PICU were viral and seasonal variation was found. Our prevalence of 37% in the patients who were screened is similar to other reviews on children with asthma exacerbations.^{15,16} Enterovirus and rhinovirus were the most frequently identified viruses and that is consistent with 2 recent large pediatric studies on patients with lower airway disease. One of the studies, however, did note that these viruses were also the most frequently found by PCR testing in control patients.^{17,18} The increased frequency of cough and fever suggest that our patients who tested positive had acute infections rather than being asymptomatic carriers. Additionally, 51% of our patients were diagnosed with enterovirus and rhinovirus by viral culture (before our laboratory changed to PCR viral testing) and that indicates active infection rather than an asymptomatic carrier.

Overall, we found a very low incidence of bacterial infections. Mycoplasma was the most common bacterium identified at 4.9% of all patients (11% of those tested), which is similar to the study by Maffey et al.⁷ Because of the delay in getting the serology results, 18% of our patients left the hospital before they were known to be IgM positive and were not treated with antibiotics. No difference in LOS was seen in this small group of patients and none of the patients with Mycoplasma was intubated or readmitted. This is in contrast to another study that suggested that not treating Mycoplasma led to readmission and increased admission to the PICU.¹⁹ That was based on 4 patients from a group who were presenting with first-time wheezing and had not been diagnosed with asthma. Our study included only patients with an established diagnosis of asthma or RAD, which may account for the difference. Based on our data, Mycoplasma appears to play a small role in status asthmaticus in the PICU and it is unclear whether patients with positive Mycoplasma IgM serology have an acute process that improves with antibiotic treatment.

Overall, 57% of the patients received antibiotics in the PICU, whereas only 19% were diagnosed with pneumonia on discharge. Many patients were started on antibiotics while awaiting the results of Mycoplasma serology. Sinusitis was also often diagnosed on discharge and that helped account for 25% of patients going home on antibiotics. Much has been written about sinusitis, lower airway disease, and whether antibiotics are needed, but that was not a focus of this study.²⁰

Multivariable logistic regression demonstrated that patients who were intubated were more likely to receive antibiotics. However, in patients where the airway was sampled, only 15% of the cultures were actually positive. Another PICU study found that only 30% of tracheal cultures were positive in intubated patients with infiltrates on CXR and suggested that there are opportunities to reduce antibiotic usage.²¹ A recent survey indicated that tracheal aspirate results are the most important factor for continuing antibiotics in intubated PICU patients.²² This was also true in our study. Generally, when the results came back negative, the antibiotics were stopped and this often occurred after the patient left the PICU.

The other major risk factor for receiving antibiotics in the PICU was a CXR reading of pneumonia. This is challenging because asthmatics often have mucous plugging and areas of atelectasis, which may appear similar to an infiltrate on a radiograph. For this study, a CXR was considered to have pneumonia only when the radiologist noted an acute

infiltrate. Another large pediatric study found that only 2.2% of afebrile children who were wheezing in the ED had radiographic findings of pneumonia.²³ We believe that our data also support that the incidence of clinical bacterial pneumonia, as diagnosed by fever and radiographic evidence of an infiltrate, is relatively low in PICU patients with status asthmaticus. Moving forward, we have removed antibiotics from our asthma order set and now have a rapid nasal *Mycoplasma* PCR test, and hope this may help reduce the use of antibiotics in the PICU.

There are limitations to this study. This is an observational, retrospective study and results need to be confirmed in larger prospective studies. Because many patients came by transport, it was not possible to have our pediatric radiologists review all the CXRs and so we had to use the radiologist's interpretation from the outside hospital in some instances. Additionally, tests for infectious pathogens were not done on all patients, so it is possible that the prevalence of these infections could be different than what is presented. However, there are few private rooms in our PICU, so patients with symptoms concerning for infection are generally screened per unit policy. Lastly, sputum cultures were rarely done and so the diagnosis of pneumonia did not include a positive respiratory culture in nonintubated patients. However, none of the sputum cultures obtained from the non-intubated patients was positive.

Conclusion

Viral infections are commonly found in patients admitted to the PICU with status asthmaticus. Patients with documented laboratory infections have a greater PICU and hospital LOS, but there is no increased rate of intubation, use of noninvasive ventilation, or length of ventilation when compared to noninfected patients. *Mycoplasma* infections appear to play a minor role in PICU patients with status asthmaticus. Antibiotics are often given for suspected bacterial or atypical pneumonia even though the true incidence is low. Although only an observational, retrospective study, factors associated with physicians prescribing antibiotics have been identified, and there appear to be opportunities for developing clear guidelines that utilize clinical indicators of infection and reduce antibiotic usage.

Author Disclosure Statement

This is original work and has not been submitted for publication to another journal. Preliminary work was presented at the 2013 SCCM meeting in San Francisco. Drs. Glenn K. Levine, Sumit Datta and Christopher J. Babbitt have no financial support or commercial associations that might create a conflict of interest in connection with the submitted article.

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