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ORIGINAL ARTICLE

Diagnosis and Management of Pediatric Influenza in the Era of Rapid Diagnostics

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Influenza is a significant cause of childhood morbidity and death; it contributes to up to 16% of hospitalizations for respiratory illnesses worldwide. Novel rapid viral diagnostic tests, including molecular diagnostic tests, have the potential to significantly affect both time to diagnosis and selection of optimal anti-infective therapy. However, little is known about current treatment algorithms used in US hospitals. In this study, for hospitalized children in the United States, we aimed to define the current approaches to influenza diagnosis and treatment and to explore reasons for their potential variation. In this study, we aimed to define the current approaches to pediatric influenza diagnosis and treatment in US hospitals, and to explore reasons for their potential variation. Our results suggest a rise in the availability and use of rapid molecular diagnostic testing in addition to continued variability in anti-infective management, particularly with regard to antiviral use.

Keywords. antimicrobial stewardship; diagnostic algorithm; influenza; oseltamivir; pediatric.

Viruses are a leading cause of acute respiratory tract infection in children, and influenza is a major source of pediatric morbidity [1]. Children in particular are susceptible to the many described complications of influenza, including lower respiratory tract involvement and bacterial coinfection, which results in significant health care resource utilization [2]. Despite recommendations for universal influenza vaccination for children ≥6 months of age and recommendations from several evidence-based guidelines for the appropriate use of antiviral medications for influenza-infected children, many children do not receive these preventive and therapeutic interventions [3].

Rapid viral diagnostic tests (RVDTs) include both rapid influenza diagnostic tests (which consist of antigen tests) and molecular diagnostic tests, which have a typical turnaround time of less than 3 hours. RVDTs can provide reliable results within minutes to hours [4] and have the potential to affect the use of anti-infectives in children with laboratory-confirmed influenza (LCI). The American Academy of Pediatrics (AAP) currently recommends the initiation of antiviral agents in all pediatric patients with LCI who require hospitalization [5]. In the absence of clear evidence of bacterial coinfection, a rapid diagnosis of LCI also should facilitate the discontinuation of unnecessary antibacterial agents. However, severely ill patients with LCI are often treated simultaneously for bacterial coinfection [6]. Thus, we hypothesize that significant variation in the anti-infective management of pediatric patients with LCI persists. In this study, we aimed to determine the different diagnostic and treatment algorithms used for LCI in the US pediatric population.

METHODS

A survey (see Supplementary Data 1) that consisted of 10 questions and incorporated 3 clinical patient vignettes was developed. The overall goal of the survey was to explore factors that lead to the use of diagnostic testing and prescription of antiviral and antibacterial therapy in hospitalized pediatric patients with influenza. The specific domains explored included type and availability of RVDT, decision making surrounding the indications for RVDT, and guideline use. The clinical vignettes were used to explore resource utilization and anti-infective use in hospitalized pediatric patients (with or without bacterial coinfection) with various degrees of illness severity. The survey was piloted among a small group of Emerging Infections Network (EIN) members and pediatric infectious diseases (PID) providers and was subsequently revised before distribution to ensure content validity, utility, clarity, and test–retest reliability. The Infectious Diseases Society of America's EIN, a provider-based emerging infections sentinel network, distributed the survey to all (n = 360) (PID) physician members in the United States and Canada via e-mail in September 2017. The EIN database maintains practice information available for each participant. The survey was distributed with an initial invitation and 2 reminders.

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For purposes of calculating the response rate, the denominator was the 341 active PID EIN members who had ever responded to an EIN survey, which is a standard methodology that has been used in previous EIN surveys [7, 8]. Respondents who reported that they did not care for children with influenza were excluded from further analyses. Respondents were not required to answer every question; thus, denominators for the individual items varied. Results were analyzed using Stata 14 statistical software. Survey responses were categorical in nature and are presented as both frequencies and percentages. Comparisons were made using both the Kruskal-Wallis test and the χ^2 test of proportions, with Fisher's exact test used where appropriate.

RESULTS

The survey was completed by 192 (56%) of 341 active pediatric EIN members, 16 of whom reported that they did not care for children with influenza and therefore did not complete the remainder of the survey. Practice data for the 192 respondents are shown in Table 1. Reported here are our findings from the remaining 176 respondents. Of these respondents, 148 (84%) reported that their institution offered molecular testing for diagnosing influenza, and 66 (37%) reported offering both a molecular and a rapid antigen test (Table 2). Most of the respondents (117 [68%]) reported that testing was available at all times of day and night. The overall availability of rapid diagnostic testing did not vary significantly between hospital types ($P = .05$). However, molecular testing was more likely to be available in university-affiliated hospitals than in non–university-affiliated hospitals (92% vs 69%, respectively; $P = .0001$). In addition, university-affiliated hospitals were more likely than non–university-affiliated hospitals to have access to testing at all times of the day or night (65% vs 35%, respectively; $P < .0001$).

Table 1. Practice Data for All Respondents

Practice Data (N = 192)	n (Column %)
US Census Bureau division for member practice location	
New England	9 (5)
Mid Atlantic	32 (17)
East North Central	27 (14)
West North Central	12 (6)
South Atlantic	29 (15)
East South Central	13 (7)
West South Central	13 (7)
Mountain	14 (7)
Pacific	39 (20)
Canada	4 (2)
Time since ID fellowship	
<5 years	41 (21)
5–14 years	66 (34)
15–24 years	41 (21)
≥25 years	44 (23)
Employment	
Hospital/clinic	58 (30)
Private/group or practice	16 (8)
University	116 (60)
Military	1 (1)
Federal government	1 (1)
Primary hospital type	
Community	11 (6)
Nonuniversity teaching	52 (27)
University	126 (66)
Federal/military hospital	3 (1)

Approximately half of the respondents reported using a guideline to direct their testing and management of pediatric influenza; 61 (35%) had their own institutional guideline, and 29 (17%) used another guideline. Respondents who used another guideline specified using the Centers for Disease Control and Prevention (CDC)/Advisory Committee on Immunization Practices, AAP, Infectious Diseases Society of America (IDSA), or New York State Department of Health guideline. We found no significant difference in the use of guidelines on the basis of hospital type ($P = .553$); however, university-affiliated hospitals were significantly more likely than non–university-affiliated hospitals to use either their own guideline (69% vs 31%, respectively; $P < .0001$) or another guideline (72% vs 28%, respectively; $P < .0001$) to assist them in their diagnosis and management.

Respondents were asked to rank the 3 factors considered most important in their decision to order an RVDT; immunocompromised state of the patient, presence of comorbidity in the patient, and the prevalence of influenza in the community were the most commonly identified factors (Figure 1).

Figure 2 shows resource utilization reported in case 1 (see Supplementary Data 1), which describes an otherwise healthy child who presented with influenza-like illness and required hospital admission. The majority of respondents (91%) opted to confirm the diagnosis with an RVDT. Despite normal examination results, more than half (57%) of the respondents reported ordering a chest radiograph, and less than half (48%) of them reported that they would recommend ordering a blood culture. Measurement of the patient's C-reactive protein/procalcitonin level was not felt necessary by the majority of respondents; only 29% of them recommended such testing. Most respondents, 111 (64%) of 176, indicated that they would treat the child described in case 1 with oseltamivir, whereas 43 (25%) of 174 reported that they would provide no therapy in this case.

For case 2, which described the same patient discussed in case 1 after a confirmed diagnosis of influenza now with superimposed bacterial pneumonia, 131 (74%) of 174 respondents reported that they would recommend oseltamivir in addition to an antibacterial medication, whereas 37 (21%) would recommend oseltamivir only. The most commonly prescribed antibacterial agents were ampicillin (65 [37%]), ceftriaxone (20 [11%]), and a combination of ceftriaxone and vancomycin (13 [7%]). This case included a follow-up question that enquired about routine use of antiviral agents on admission for hospitalized pediatric patients with LCI. For this question, 90 (52%) of the respondents selected

Table 2. RVDT According to Availability and Type

Type and Availability	N (%)	University-Affiliated Hospitals (n/N [%])	Non–University-Affiliated Hospitals (n/N [%])	*P*
Type of RVDT used (n = 176)				
Antigen test only	24 (14)	8/24 (33)	16/24 (67)	.0004
Molecular test only	82 (47)	66/82 (80)	16/82 (20)	<.0001
Both antigen and molecular tests	66 (37)	39/66 (59)	27/66 (41)	.002
Not sure	1 (1)	0/1 (0)	1/1 (100)	NA
None	3 (2)	1/3 (33)	2/3 (67)	.21
RVDT availability (n = 173)				
All times of day and night	117 (68)	76/117 (65)	41/117 (35)	<.0001
Weekdays and weekend days	26 (15)	14/26 (54)	12/26 (46)	.41
Weekdays, weeknights, and weekend days	7 (4)	5/7 (71)	2/7 (29)	.01
Other	3 (2)	1/3 (33)	2/3 (67)	.23
Weekdays only	11 (6)	8/11 (73)	3/11 (27)	.0006
Not sure	9 (5)	8/9 (89)	1/9 (11)	<.0001

Abbreviations: NA, not applicable; RIDT, rapid influenza diagnostic test; RVDT, rapid viral diagnostic testing.
[a]The term RVDT includes both RIDTs and molecular testing with a turnaround time of <3 hours.

the response "all pediatric patients," followed by the selection of 4 options (within 48 hours of symptom onset, critically ill children, immunocompromised children and children with comorbidities) by 23 (13%). The remaining 35% of the respondents chose a different combination of the remaining responses (see Supplementary Data 1, question 9). Case 3 explored the decision on whether to continue antibacterial therapy after 48 hours in a critically ill child with influenza on oseltamivir for whom no clear evidence of bacterial infection was found with serial chest radiography or culture. Here, the majority of respondents (104 [60%]) reported that they would not prescribe any antibacterial therapy, whereas 22 (13%) reported that they would recommend ceftriaxone and vancomycin. The remaining 27% of respondents chose one of the following; ceftriaxone (11%), ampicillin alone (6%), ampicillin-sulbactam (3%), ceftriaxone and clindamycin (2%), clindamycin (2%), vancomycin (1%) or another antibacterial agent (2%).

DISCUSSION

Compared with previously published data [9], the results of our nationwide survey of US PID providers suggest substantial evolution over the past 5 years in the management of hospitalized children with influenza. First, we found that molecular testing is now widely available in pediatric centers in the United States, at all times of the day and night. Overall, 84% of the respondents reported having either PCR testing or both PCR and rapid antigen testing available to them, compared with the most recent estimate of 26%, based on a survey of 240 laboratories participating in the Influenza Hospitalization Surveillance Network (FluSurv-NET) during the 2012–2013 influenza season. This FluSurv-NET study, which included a combination of academic institutions, children's hospitals, and general hospitals, revealed that only 13% of participating hospitals at that time were using

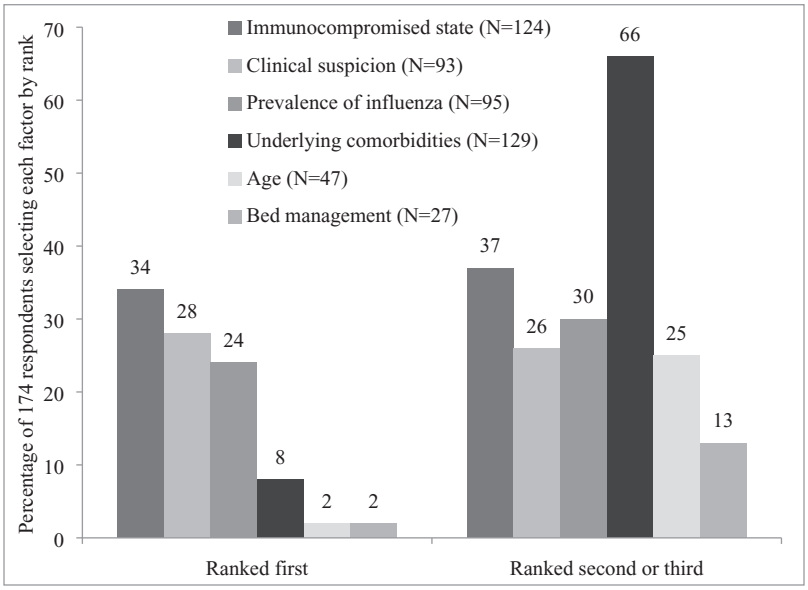

Figure 1. Factors ranked as most important when ordering a rapid viral diagnostic test.

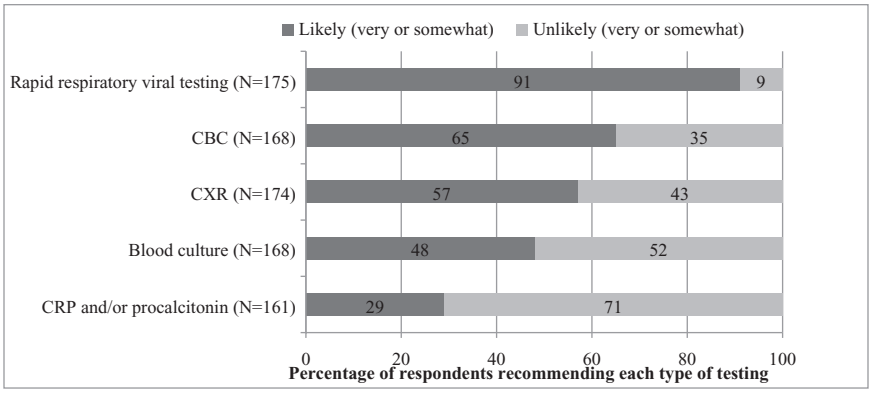

Figure 2. Resource utilization in an otherwise healthy child with uncomplicated influenza. Abbreviations: CBC, complete blood count; CRP, C-reactive protein; CXR, chest radiograph.

PCR testing for diagnosing inpatients with influenza, which suggests a nationwide increase in the use of molecular testing for the diagnosis of influenza.

Another important result of this national survey is that many more practitioners, approximately half of all the respondents, reported the use of evidence-based guidelines to direct their testing and management. The majority (80%) of hospitals participating in FluSurv-NET had reported previously that they did not have a policy in place to systematically test patients with acute respiratory infection who present during influenza season [9]. This increased use of guidelines might account for the resource utilization pattern outlines in Figure 2; where the majority of respondents opted for RVDT confirmatory testing, and far fewer reported measurement of C-reactive protein or procalcitonin levels in the absence of a strong suspicion for bacterial infection.

Our survey revealed that inconsistencies persist in the use of oseltamivir in previously healthy children who are hospitalized. We found that despite approximately 91% of the respondents confirming the diagnosis of influenza with RVDT, only 65% of them would recommend oseltamivir as treatment for an otherwise healthy hospitalized child without evidence of complications. In addition, only 74% of them would opt to recommend oseltamivir in addition to an antibiotic for a child with evidence of bacterial coinfection as a complication. This result did not differ significantly according to type of hospital or years of experience of the respondent. It is important to note that all of the noninstitutional guidelines the respondents reported using, including those of the CDC/Advisory Committee on Immunization Practices, IDSA, and AAP [5, 10, 11], continue to recommend initiation of antiviral therapy in children hospitalized with influenza. Early treatment has been associated with an observed reduction in the severity and duration of symptoms in addition to decreased rates of complications including bacterial coinfection [6]. In critically ill pediatric patients, early initiation of a neuraminidase inhibitor within 24 to 48 hours of hospitalization was associated with both a decreased number of deaths [12] and a reduction in total hospital days [13]. Despite this, the initiation of antiviral therapy has not gained universal acceptance with variations in management existing among providers, likely due to debate surrounding its utility in otherwise healthy children [14] and concerns about side effect profile [15, 16].

Although oseltamivir-prescribing trends have varied significantly in the United States since the 2009 H1N1 pandemic, the results of our survey are consistent with recent estimates. Between 2012 and 2014, oseltamivir use was described to be as high as 82% in hospitalized children in the United States [17]. However, most recently, Stockmann et al [18] demonstrated a high level of variation and suboptimal use of antivirals in hospitalized children, with an overall proportion of antiviral prescribing of 69%. Importantly, there was only a slight increase in the rate of prescribing for children with high-risk conditions. Our findings add to the body of evidence that highlights the need for ongoing education surrounding prompt initiation of antivirals in children with influenza.

Last, our survey highlights progress toward an overall judicious approach to the use of antibacterial agents in children hospitalized with influenza. For case 2, a majority of the respondents opted to treat superimposed bacterial pneumonia with ampicillin. Despite the well described association of a co-infection with *Staphylococcus aureus* and *Haemophilus influenzae* in patients with influenza [19], *Streptococcus pneumoniae* is the most frequently isolated bacterial pathogen and its presence has been documented to correlate with severity of illness [20]. Clinical practice guidelines from the Pediatric Infectious Diseases Society and the IDSA recommend ampicillin as first-line therapy for any previously healthy immunized child older than 3 months who is admitted to the hospital with a diagnosis of community-acquired pneumonia [21]. In our clinical vignette, ampicillin is an appropriate choice of therapy; however, we acknowledge the challenges encountered when treating a child with a more complex presentation, when providers might feel the need to broaden therapy to include an antistaphylococcal agent.

For case 3, which described a critically ill child without evidence of bacterial infection after 48 hours, 60% of the respondents

reported a preference for no antibiotics. It is important to note that respondents commented that this decision should be made in conjunction with ICU physicians, who may wish to continue them in the face of critical illness. Data in adults without evidence of bacterial coinfection have revealed similar outcomes among patients admitted with severe influenza who received empiric treatment courses of antibiotics and those who did not. Increased colonization with multidrug-resistant organisms was noted also [22]. With the lack of benefits and documented risks known to pertain to prolonged antibacterial use in this setting, there remains a need to continue educating and involving PID physicians in the management of infective complications in critically ill children.

Our survey has some limitations. Although we are satisfied with our overall response rate, we acknowledge the possibility of response bias. We realize that although our clinical vignettes simulate typical presentations of pediatric influenza, they cannot substitute for real-life scenarios, which need to be considered on a case-by-case basis. Last, the responses to this survey represent the opinions of PID providers who are typically involved in consultation, not as front-line clinicians. That said, infectious disease providers are heavily involved in the development of guidelines surrounding the best practices for pediatric patients with influenza and are expected to be up to date with their institution's approach to influenza diagnosis and treatment.

CONCLUSION

The results of this national study on diagnostic and management approaches to hospitalized pediatric patients with influenza highlight some key points, including (1) the rise in availability of molecular testing, (2) an overall suboptimal but stable postpandemic percentage of antiviral prescribing, and (3) a preference for an overall judicious approach to the administration of antibacterial agents by infectious disease physicians. Our results also highlight the important role that guidelines play in the diagnosis and management of pediatric influenza. With the access to rapid diagnostics increasing nationwide, we advocate for a standardized approach to management with a focus on improved stewardship efforts regarding appropriate antiviral use and antibacterial management. At a time when the surge of antimicrobial resistance represents a very real public health threat, there remains an opportunity for education on the spectrum of severity of influenza to increase the prompt prescribing of antiviral agents and to ensure the appropriate prescribing of antibacterial agents in hospitalized pediatric patients.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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