

Admission diagnoses of children 0–16 years of age hospitalized with influenza

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Abstract The prompt diagnosis of influenza enables the institution of antiviral therapy and adequate cohorting of patients, but scarce data are available to help clinicians correctly suspect influenza in children at the time of admission. This 16-year retrospective study assessed the main admission diagnoses of 401 children aged ≤ 16 years hospitalized with virologically confirmed influenza. The clinical data were derived from a systematic review of the medical records of the children. Sepsis-like illness was the main reason for admission in 52% of infants aged <6 months and in 7–16% of the older children. Respiratory symptoms accounted for 38% of admissions, and 15% of children were hospitalized due to acute neurologic conditions, primarily febrile convulsions. Wheezing or exacerbation of asthma was the primary reason for admission in 14% of children aged <3 years. No differences were observed in the admission diagnoses between children with influenza A and B infections. The main admission diagnoses vary widely in different age

groups of children with influenza, and only a minority of children are hospitalized for respiratory symptoms. The leading role of sepsis-like illness in infants aged <6 months calls for increased efforts to find protective measures against influenza in this age group.

Introduction

Annual influenza epidemics bring about a substantial disease burden on children, and influenza-related complications are frequent especially among the youngest patients [1–8]. Although the vast majority of children with influenza are treated as outpatients, the rates of influenza-associated hospitalizations are high in children, particularly among those younger than 2 years of age [1, 2, 7–10].

The clinical spectrum of influenza ranges widely from an asymptomatic infection to a life-threatening illness. Although the hallmark symptoms of influenza are high fever and cough, influenza may also manifest itself, e.g., as a severe form of croup, and, occasionally, febrile convulsion may be the first sign of influenza in young children [11–13]. Furthermore, the clinical features of influenza in children vary with age [14].

Few previous studies have assessed the clinical presentation of seasonal pediatric influenza at the time of hospital admission [15, 16]. Such information would be important for the clinician because the prompt identification of influenza-infected children enables the institution of early antiviral treatment and proper cohorting of patients on wards [17, 18]. We sought to determine the main admission diagnoses of children in different age groups who were hospitalized with laboratory-confirmed influenza during a 16-year study period.

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Patients and methods

Study design and subjects

We conducted this retrospective study at the Department of Pediatrics, Turku University Hospital, Turku, Finland, during a period of 16 consecutive years from July 1, 1988, through June 30, 2004. Turku University Hospital is the only tertiary-care hospital in Southwestern Finland and the sole provider of acute pediatric hospital care for approximately 69,000 children ≤ 16 years of age. The study population consisted of all children aged ≤ 16 years who were hospitalized with virologically confirmed influenza during the study period.

Data collection and viral diagnosis

To identify all children who were hospitalized with influenza, we searched for data from three different sources: (1) the Department of Virology, University of Turku, which was the only laboratory that provided routine viral diagnostic services for our hospital; (2) the central database of Turku University Hospital; and (3) the files of the pediatric infectious diseases ward at our hospital. The medical records of all children with an International Classification of Diseases (ICD) code related to influenza (ICD-9: 4870A, 4871A, and 4878X; ICD-10: J10–J11) who were not found from the database of the Department of Virology were carefully examined to confirm or rule out the viral diagnosis of influenza. The files of the pediatric infectious diseases ward were examined to identify children who had tested positive for influenza by a rapid influenza test and from whom no additional viral specimens had, therefore, been obtained. Overall, we found 407 children who were hospitalized with virologically confirmed influenza. Six children were excluded from this analysis because the viral specimens had been obtained >2 days after admission, and, hence, nosocomial influenza infection could not be ruled out. The final analyses consisted of 401 influenza virus-infected children. The viral diagnosis was based on antigen detection [19] or viral culture in 372 (93%) cases and on rapid influenza testing (Directigen FluA+B, Becton Dickinson Diagnostic Systems, Sparks, MD, USA) in 29 (7%) cases. Seven children each were admitted twice due to influenza during the study period.

Classification of admission diagnoses and definitions

We categorized the primary reasons for admission into nine groups based on the presenting signs and symptoms and any additional information found in the medical records: (1) sepsis-like illness; (2) respiratory infection; (3) acute neurologic condition; (4) muscular symptoms; (5) abdom-

inal symptoms; (6) general condition; (7) severe underlying condition; (8) social indication; and (9) other concomitant illness. The clinical data were collected by a systematic chart review, and, for consistency, the main reason for admission was determined by one investigator (H.S.) according to all of the available data. The primary admission diagnosis of a child could be different from the official discharge diagnosis recorded in the hospital central database. A few children had two or more apparent reasons for hospitalization; in these cases, the children's medical charts were re-reviewed (by H.S. and T.H.) for consensus.

The diagnosis of pneumonia was based on radiological confirmation of the condition at admission. The admission diagnosis was recorded as upper respiratory tract infection if the child was hospitalized with a respiratory illness other than pneumonia, asthma/wheezing, laryngitis, tracheitis, or epiglottitis. Prolonged fever was defined as fever that had lasted ≥ 5 days. Vomiting was recorded as the main reason in case of repeated vomiting without signs of dehydration. Neurologic defects included severe, mainly congenital neurologic diseases, for example, cerebral palsy and tuberous sclerosis. The category "social indication" was used for children who were admitted mainly because of social problems and not because of the severity of the illness. Most children in the category "other concomitant illness" had a febrile respiratory illness, but the respiratory symptoms were not considered as the main reason for hospitalization.

Statistics

The Chi-square test and the Mann–Whitney *U*-test were used for comparisons between different groups of children. Two-sided *p*-values <0.05 were considered to be statistically significant. All statistical analyses were performed with StatsDirect (version 2.7.7) software.

Results

Study population

The median age of the 401 children in the study was 1.6 years (mean, 3.5 years; range, 1 week to 16 years). Eighty-eight (21.9%) children were <6 months of age; 169 (42.1%) were 0.5–2.9 years of age; 71 (17.7%) were 3.0–6.9 years of age; and 73 (18.2%) were 7.0–16.9 years of age. A total of 222 (55.4%) children were boys. One-hundred and five (26.2%) children had an underlying chronic illness, with asthma being the most common condition (7.2% of all children), followed by neurologic defects (6.7%) and malignancy or immunosuppression (4.2%). Influenza A virus was detected in 330 (82.3%)

children and influenza B virus in 70 (17.5%) children; one child was infected with influenza A and B viruses simultaneously.

Primary admission diagnoses in different age groups

The primary admission diagnoses of children in different age groups are presented in Table 1.

In the entire child population, the most frequent reason for admission was respiratory illness, which accounted for 38% of all influenza-related admissions; approximately one-third of these children had pneumonia. Sepsis-like illness was the main reason for hospitalization in 52% of infants <6 months of age, but also in 7–16% of children in the older age groups. Wheezing or exacerbation of asthma was the primary reason for admission in 14% of infants and children <3 years of age. Twelve percent of all children were hospitalized due to febrile convulsion. Overall, 15% of the children were admitted because of acute neurologic symptoms and 10% because of dehydration.

Admission diagnoses in children with influenza A and B infections

The rates of different admission diagnoses were further analyzed according to the type of influenza virus; one child with simultaneous infection with influenza A and B viruses was excluded from this analysis. Because the median ages of children with influenza A and B infections were significantly different (influenza A, 1.5 years; influenza B, 5.5 years; $p < 0.001$), the relative proportions of various admission categories were compared within each of the four different age groups (Fig. 1). No significant differences were observed in any categories between children with influenza A and B infections in any of the age groups.

Discussion

Our study demonstrates the wide spectrum of clinical conditions seen in influenza virus-infected children at the time of hospitalization. Furthermore, our results show that the main admission diagnoses vary substantially between different age groups of children. Although some previous studies have described the clinical features and outcomes in children hospitalized with seasonal influenza [15, 16], to our knowledge, this is the first study to assess and compare the admission diagnoses between different age groups of children who are being hospitalized with virologically confirmed influenza.

Perhaps the most striking finding in our study was that more than half of all infants under 6 months of age were admitted due to sepsis-like illness. In this age

group, full-blown respiratory symptoms are often absent during the early phase of the illness, and the first manifestation of influenza may be an abrupt onset of high fever that imitates bacterial sepsis [7, 20–22]. Although the true incidence of serious bacterial co-infections in influenza virus-infected infants is low [22, 23], the presence of high fever in young infants usually leads to invasive examinations, hospitalization, and empirical antibiotic treatment [15]. Altogether, these procedures generate a notable burden on infants and their families, as well as substantial costs on society [24, 25]. In a recent US study of children <5 years of age with virologically confirmed influenza, hospitalized infants <6 months of age accounted for 45% of the total costs of influenza [25].

Although influenza is principally a respiratory infection, it was surprising that only 38% of the children were admitted mainly for respiratory symptoms. This finding is important, as it could be assumed that children with primarily non-respiratory clinical manifestations may easily remain undiagnosed and, subsequently, not receive adequate treatment for their influenza. The clinical importance of the early identification of influenza was underscored by our recent trial that demonstrated that oseltamivir treatment started within 24 h of the onset of influenza symptoms shortened the duration of illness by 3.5–4 days in young children with influenza A infection [18].

Compatible with earlier reports [26–30], pneumonia was the most frequent respiratory diagnosis leading to the hospitalization of children older than 6 months of age; one-sixth of all children in this age group were admitted due to suspected bacterial pneumonia. Although rhinoviruses and respiratory syncytial virus have been shown to be the most frequent etiologic agents in acute wheezing and exacerbation of asthma in young children [31], it is worth noting that acute expiratory wheezing was the primary reason for admission in approximately 14% of children <3 years of age, which suggests that the role of influenza viruses in triggering acute wheezing attacks in children is far from negligible. Furthermore, 5% of all influenza admissions were due to laryngitis, which is in agreement with a previous report indicating that laryngitis caused by influenza viruses is more severe than that caused by parainfluenza viruses [12].

Acute neurologic symptoms accounted for 15% of all influenza-related hospitalizations, which is a remarkably high percentage for a respiratory infection. This finding is, however, in good accordance with previous studies that have demonstrated an increased risk for influenza-related neurologic complications, mainly seizures, in young children [15, 32, 33]. Chiu et al. reported that influenza infections were associated with a higher incidence of febrile seizures than adenovirus or parainfluenza virus infections [13]. In our study, the rate of febrile convulsions was

Table 1 Main admission diagnoses of 401 children with virologically confirmed influenza in different age groups

Category	<6 months		0.5–2.9 years		3.0–6.9 years		7.0–16.9 years		Total	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Sepsis-like illness	46	(52.3)	12	(7.1)	8	(11.3)	12	(16.4)	78	(19.5)
Suspected sepsis	46	(52.3)	11	(6.5)	6	(8.5)	10	(13.7)	73	(18.2)
Suspected meningitis	0		1	(0.6)	2	(2.8)	2	(2.7)	5	(1.2)
Respiratory infection	25	(28.4)	88	(52.1)	22	(31.0)	16	(21.9)	151	(37.7)
Pneumonia	1	(1.1)	31	(18.3)	14	(19.7)	7	(9.6)	53	(13.2)
Asthma/wheezing	13	(14.8)	23	(13.6)	2	(2.8)	0		38	(9.5)
Upper respiratory infection	8	(9.1)	18	(10.7)	4	(5.6)	6	(8.2)	36	(9.0)
Laryngitis	3	(3.4)	14	(8.3)	1	(1.4)	3	(4.1)	21	(5.2)
Tracheitis	0		1	(0.6)	1	(1.4)	0		2	(0.5)
Epiglottitis	0		1	(0.6)	0		0		1	(0.2)
Acute neurologic condition	3	(3.4)	31	(18.3)	9	(12.7)	18	(24.7)	61	(15.2)
Febrile convulsion	3	(3.4)	30	(17.8)	7	(9.9)	7	(9.6)	47	(11.7)
Vertigo/collapsus	0		0		0		6	(8.2)	6	(1.5)
Encephalitis	0		0		1	(1.4)	3	(4.1)	4	(1.0)
Non-febrile convulsion	0		1	(0.6)	1	(1.4)	1	(1.4)	3	(0.7)
Confusion	0		0		0		1	(1.4)	1	(0.2)
Muscular symptoms	0		2	(1.2)	2	(2.8)	5	(6.8)	9	(2.2)
Myositis	0		0		1	(1.4)	4	(5.5)	5	(1.2)
Myalgia	0		2	(1.2)	1	(1.4)	1	(1.4)	4	(1.0)
Abdominal symptoms	1	(1.1)	0		0		3	(4.1)	4	(1.0)
Pain	1	(1.1)	0		0		2	(2.7)	3	(0.7)
Vomiting	0		0		0		1	(1.4)	1	(0.2)
General condition	9	(10.2)	21	(12.4)	15	(21.1)	7	(9.6)	52	(13.0)
Dehydration	8	(9.1)	16	(9.5)	11	(15.5)	6	(8.2)	41	(10.2)
Prolonged fever	1	(1.1)	5	(3.0)	4	(5.6)	1	(1.4)	11	(2.7)
Severe underlying condition	0		6	(3.6)	4	(5.6)	5	(6.8)	15	(3.7)
Neurologic defect	0		4	(2.4)	3	(4.2)	3	(4.1)	10	(2.5)
Other ^a	0		2	(1.2)	1	(1.4)	2	(2.7)	5	(1.2)
Social indication	1	(1.1)	4	(2.4)	0		1	(1.4)	6	(1.5)
Other concomitant illness	3	(3.4)	5	(3.0)	11	(15.5)	6	(8.2)	25	(6.2)
Pyelonephritis	2	(2.3)	2	(1.2)	2	(2.8)	2	(2.7)	8	(2.0)
Suspected Kawasaki disease	0		1	(0.6)	1	(1.4)	0		2	(0.5)
Urticaria	0		0		2	(2.8)	0		2	(0.5)
Suspected carditis	0		0		1	(1.4)	1	(1.4)	2	(0.5)
Other ^b	1	(1.1)	2	(1.2)	5	(7.0)	3	(4.1)	11	(2.7)
Total	88	(100)	169	(100)	71	(100)	73	(100)	401	(100)

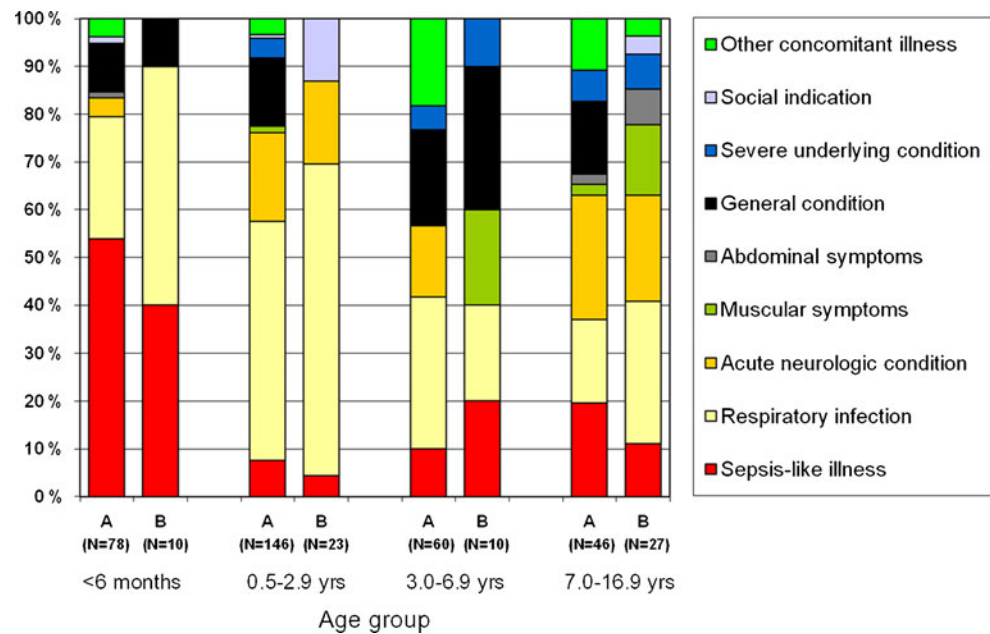
^a One each of: congestive heart failure; status post-meningococcal sepsis; autoimmune neutropenia; status post-liver transplantation; diabetes in poor balance

^b One each of: perianal condylomas; prophylaxis for meningococcal disease; new-onset diabetes; tympanostomy tube placement; bone marrow donation; epistaxis; glycosuria; hypoglycemia; concussion; tachycardia; periorbital cellulitis

especially high among children aged 6 months to <3 years. Combined with other data evidencing that the total disease burden of influenza is greatest in children younger than 3 years of age, our findings corroborate the view that young children would substantially benefit from influenza vaccination [4, 34, 35].

It is generally thought that the clinical features of influenza A and B infections are different, with influenza A viruses causing more severe illnesses than influenza B viruses. While there are undoubtedly substantial differences in the overall virulence between different strains of influenza circulating in different years, it is possible that

Fig. 1 Relative proportions of different admission categories in children with influenza A and B infections in different age groups



the conventional concept of an overall difference between A and B viruses is seriously confounded by age. In several studies, including the present one, children hospitalized with influenza B infections have been significantly older than those with influenza A infections [10, 16], and few studies have attempted to adjust the clinical features for the age of the children. In this study, in which we analyzed the admission diagnoses separately in different age groups, we could not demonstrate any significant differences between influenza A and B infections. This finding tends to agree with our earlier prospective study among outpatients, in which no differences were observed in any signs or symptoms between children with influenza A or B virus infections when analyzed within different age groups [14].

The main strengths of our study include the careful structured analysis of the medical records of all children and the 16-year observation period that balances any potential year-to-year variation in the results. There are also some limitations. Although obtaining viral specimens from hospitalized children was a routine procedure at our department during the period of this study, it is possible that some children with influenza had not been subjected to viral sampling. It is also possible that, especially with rapid diagnostic tests, some of the tests have remained false-negative. However, because of the generally high specificity of influenza rapid tests, we believe that, regardless of the viral diagnostic method used, all of the children in our analysis had true influenza, which is the most important issue for this study. In a few cases, the allocation of children into the different admission diagnosis categories was challenging due to the retrospective nature of the study.

This was particularly true for children with underlying conditions, some of whom had two or more potential admission diagnoses available. Overall, however, we consider it very unlikely that any of these shortcomings could have introduced a significant bias to the results.

Infants younger than 6 months of age are an extremely vulnerable group in regard to seasonal influenza because neither vaccines nor antiviral treatments are currently available for them. Some recent studies have provided encouraging initial evidence for the safety and immunogenicity of a trivalent inactivated influenza vaccine in infants as young as 2 months of age [36, 37], but further studies in this area are clearly needed. In the meantime, readily available options to diminish the burden of influenza in the youngest infants include the immunization of mothers during pregnancy and the vaccination of all family members and close contacts of the infants [38–40].

In conclusion, we found that the clinical presentation of influenza varied widely in different age groups of children at the time of hospital admission. Our findings provide a challenge to clinicians who are responsible for the optimal treatment of these patients, and the results underscore the importance of clinicians' awareness of the full spectrum of clinical manifestations of influenza in children. The leading role of sepsis-like illness in infants younger than 6 months of age is important, and further research into effective protective measures against influenza in this age group is clearly warranted.

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Conflict of interest statement The authors declare that they have no conflict of interest.

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