ORIGINAL ARTICLE

Clinical characteristics of children and adults hospitalized for influenza virus infection

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Background/Purpose: Influenza infection has different clinical presentations and outcomes in children and adults, and bacterial coinfection is associated with significantly higher morbidity and mortality. This study compared the clinical features in children and adults hospitalized for influenza virus infection and the role of concomitant bacteremia.
Methods: A retrospective observational cohort study was conducted by a review of medical records of all consecutive patients admitted for influenza infection between April 1, 2009 and February 28, 2011.
Results: Of the 1203 patients, 76.2% were children, and ranged in age from 1 month to 99 years, with a mortality of 3.1% for adults; no children died. Pneumonia, acute respiratory distress syndrome, acute respiratory failure, septic shock, and cardiovascular complications were more common in adults. Bacteremia was more common in adults than in children (3.5% vs. 0.4%). C-reactive protein (CRP) > 4 mg/dL and a longer hospital stay occurred more often in children with bacteremia than in the group without bacteremia. In adults with bacteremia, acute respiratory failure, septic shock, and cardiovascular complications were more common, with a mortality of 50% versus 1.4% compared with those without bacteremia, and thrombocytopenia and increased CRP were independent risk factors. Using receiver operating characteristic analysis, CRP ≥ 14 mg/dL had a sensitivity of 90.0% and a specificity of 80.0%.

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Conclusion: Influenza infection in adults is associated with increased risk of complications, bacteremia, and mortality compared with that in children. Bacteremia in adults with influenza is associated with increased complications and mortality; thrombocytopenia and elevated CRP levels could identify those at risk.

Background

Influenza is an acute infectious respiratory disease of viral cause that occurs annually in outbreaks, epidemics, and occasionally pandemics of varying severity and attack rates depending on the influenza virus subtype involved.[1] Even though the mortality associated with epidemics is relatively low, the total number of fatalities may be huge.[2] In the recent pandemic, influenza A H1N1 virus has been estimated to cause 18,499 deaths in 214 different countries for the period April, 2009 to August 1, 2010.[3] The very young, the very old, and persons with chronic medical conditions (pulmonary, cardiovascular, liver, renal and neurologic diseases, diabetes mellitus, or immunosuppression) have an increased risk of hospitalization and mortality from influenza virus infection.[2,4] In the setting of a severe pandemic, hospitals face an enormous burden of patients, with a huge influx of individuals requiring intensive care.[5] Influenza also imposes a huge financial burden on healthcare systems and society overall.[1]

Bacterial coinfection in influenza virus infection has been associated with significantly higher morbidity and mortality among patients in the intensive care unit.[6] Data on pediatric mortality associated with influenza in the United States have shown an increase in the rate of bacterial coinfection, from 6—36% between 2004—2005 and 2006—2007.[7] Severe complicated influenza infection, defined by influenza-like illnesses with evidence of pneumonia, neurologic symptoms, myocarditis, pericarditis, or invasive bacterial infection, has been a notifiable disease in Taiwan since 2003.[8] Children and adults have different clinical presentations and outcomes in influenza infection, and many studies on bacterial coinfection in influenza virus infection have focused on bacterial pneumonia, whereas only a few dealt with concomitant bacteremia.

The purposes of this study were to first compare the risk factors, clinical features, and complications in children and adults hospitalized for influenza infection, and second, to determine the clinical features and role of concomitant bacteremia in these patients.

Methods

Study setting

Mackay Memorial Hospital is a 2000-bed tertiary referral hospital in Taiwan, with 54 beds in the adult medical intensive care unit and 19 beds in the pediatric intensive care unit.

This retrospective, observational cohort study was conducted by reviewing the medical records of all consecutive patients admitted for influenza infection between April 1, 2009 and February 28, 2011. Only patients with clinical features of influenza, and diagnosis confirmed by positive rapid antigen test, virus culture, or real-time polymerase chain reaction test were included. Patients with inadequate medical records were excluded. This study was approved by the institutional review board of our hospital.

Definitions

Children were defined as age 18 years or younger, and adults were older than 18 years. Data were collected by reviewing the medical records and included demographic characteristics, medical history, and laboratory data, including antimicrobial susceptibility data. Risk factors for severe complications from influenza were defined based on those listed by the United States Advisory Committee on Immunization Practices.[9] These risk factors included chronic pulmonary (including asthma) or cardiovascular (excluding hypertension), renal, hepatic, neurological/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus), immunosuppression; and residency in nursing homes and other long-term care facilities.[9] Immunocompromised status was defined as the presence of a hematologic malignancy, active cancer, or human immunodeficiency virus infection, or treatment with long-term corticosteroids, immunosuppressive therapy, or cytotoxic chemotherapy. In patients with bacteremia, data were collected from blood cultures done at presentation or within 24 hours of admission and during the course of their hospital stay. In adults, leukopenia was defined as a total white blood cell (WBC) count $< 4000/\mu L$ and thrombocytopenia as a total platelet count $< 100 \times 10^3/\mu L$. In children, leukopenia was defined as a total WBC count $< 4000/\mu L$ and thrombocytopenia as a total platelet count $< 100 \times 10^3/\mu L$. Elevated plasma C-reactive protein (CRP) was defined as CRP > 1 mg/dL. In adults, sepsis was defined as a documented infection with one or more of the following: core temperature $> 38.3°C$ or $< 36°C$, heart rate > 90 beats/minute, respiratory rate > 20 breaths/minute or partial pressure of CO_2 in arterial blood ($PaCO_2$) < 32 mm Hg, and a WBC count $> 12,000/\mu L$ or $<4000/\mu L$ or $>10\%$ band forms. In children, sepsis was defined as signs and symptoms of inflammation plus infection with hyperthermia or hypothermia, tachycardia, and at least one of the following indications of altered organ dysfunction: altered mental state, hypoxemia, increased serum lactate levels, or bounding pulses. Septic shock was defined as sepsis with acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes (following the criteria of the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference).[10] Clinically significant

bacteremia or bloodstream infection (BSI) was defined as the isolation of bacteria from one or more blood cultures from a patient with associated relevant symptoms and signs of systemic infection. Bacteremia was considered to be community-acquired if a blood culture that yielded positive findings was obtained within 48 hours of hospital admission, and was not associated with any procedure performed after hospital admission; and healthcare-associated (HCA) if the blood culture was obtained more than 48 hours after hospitalization. The BSIs caused by coagulase-negative staphylococci and other bacteria of saprophytic skin flora were excluded. Severity of illness was assessed by means of the acute physiology and chronic health evaluation (APACHE) II score.

Statistical analysis

All the analyses were performed using SPSS 15 (SPSS Inc., Chicago, IL, USA). Patients' characteristics were expressed either as mean $\pm$ standard deviation with interquartile range (IQR; continuous variables) or frequency with percentage (categorical variables). Subgroup analysis was performed among adult patients. Characteristics between different groups were further compared using Student t test or Fisher's exact test as appropriate. Variables with $p < 0.05$ by bivariate analyses were further included in the multivariate regression model. Logistic regression was applied to identify the risk factors for bacteremia. The results were presented as odds ratios (OR) and their corresponding 95% confidence intervals (CI).

Results

From April 1, 2009 to February 28, 2011, 7782 patients were treated at the emergency department and as outpatients, and 1360 patients were hospitalized for laboratory-confirmed viral influenza infection at our hospital. After excluding patients with inadequate medical records; data from 1203 patients hospitalized for influenza infection were available for analysis. As shown in Fig. 1, trends of influenza infection over the study period were similar between pediatric and adult patients. The highest monthly incidences recorded were from August 2009 to November 2009, and in January 2011.

Demographic and clinical characteristics of children and adults hospitalized for influenza infection are shown in Table 1. The age range was from 1 month to 99 years, and children made up 76.2% of the hospitalized individuals.
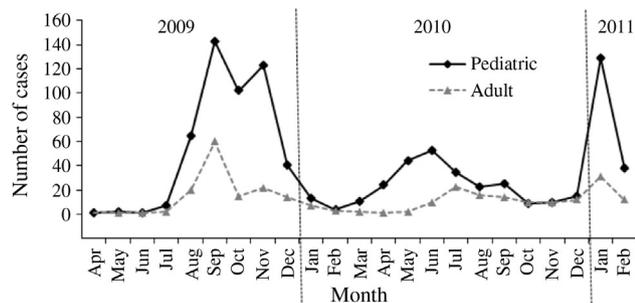

Figure 1. Monthly incidence of influenza infection in children and adults during the study period.

Influenza A was the predominant type in both adults and children, and more male children than adults were hospitalized for influenza. Overall, 67.7% ($n = 814$) of the patients, including 72.5% ($n = 665$) of children and 52.1% ($n = 149$) of adults, had no risk factors, whereas among adults, 12.2% ($n = 35$) had two or more risk factors compared with 4.4% of children ($n = 40$). In children, chronic lung disease (bronchial asthma) was the most common risk factor, followed by neurologic disease and heart disease; in adults, diabetes mellitus was the most common risk factor, followed by chronic lung disease, heart disease, and neurologic disease. Thrombocytopenia, increased CRP, pneumonia, acute respiratory distress syndrome (ARDS), acute respiratory failure, septic shock, cardiovascular complications, and bacteremia occurred more often in adults than in children. More adults required intensive care unit (ICU) admission, extracorporeal membrane oxygenation (ECMO) use, and a longer hospital stay than in children. Mortality was 3.1% for adults, whereas no children died of influenza infection. Oseltamivir was the only antiviral agent used in all patients, including 95.1% of children (872 of 917), and all adults.

CRP > 4 mg/dL and a longer hospital stay were more common in children with bacteremia than in those without bacteremia (Table 2). None of the children with bacteremia had complications or required ICU admission. Bacteremia occurred in 10 adults and was more common in influenza B than influenza A (3 of 17, 17.7% vs. 7 of 269, 2.6%, respectively, $p = 0.001$) Adults with bacteremia were older, and liver cirrhosis was more common than in those without bacteremia, as were leukocytosis, thrombocytopenia, and elevated CRP > 4 mg/dL (60.0% vs. 18.8%, 44.4% vs. 3.4% and 90.0% vs. 47.0%, respectively). Acute respiratory failure, cardiovascular complications, septic shock, use of ECMO and longer ICU stay were also more common in adults with bacteremia, who also had an increased mortality (50.0% vs. 1.4%) compared with the nonbacteremic group.

Children with bacteremia had no risk factors, and all had influenza A virus infection and community-acquired bacteremia (Table 3). The bacteria isolated most often in children was *Streptococcus pneumoniae* ($n = 2$, 50.0%). All were treated with oseltamivir, and 75.0% (3 of 4) received antibiotics. One or more risk factors were present in 70.0% of adults (7 of 10) with bacteremia (Table 4), and 70.0% (7 of 10) had influenza A virus infection. The most common risk factors were cardiovascular disease and diabetes mellitus ($n = 4$, 40.0% for both), followed by kidney disease and liver cirrhosis ($n = 3$, 30.0% for both). The bacteria isolated most often in adults were *Acinetobacter baumannii* and *Escherichia coli* ($n = 3$, 30.0% for both). In adults, 90.0% of BSI (9 of 10 patients) was community-acquired. HCA infection was present in two patients with bacteremia who died: patient Number 4 had *A. baumannii* bacteremia; and patient Number 8 initially had community-acquired BSI with *Serratia marcescens*, and later developed HCA infection with *A. baumannii* bacteremia. The other three adults with bacteremia who died had community-acquired BSI: patient Number 1 had *Enterobacter cloacae* (extended spectrum β-lactamase (ESBL) strain) bacteremia; patient Number 7 had *A. baumannii* bacteremia, and patient Number 10, who was initially treated at a local medical dispensary with oseltamivir without antibiotic use,

Table 1 Demographic and clinical characteristics of children and adults hospitalized for viral influenza[a]

Variables	Children (n = 917)	Adults (n = 286)	Total (n = 1203)	p
Age (y)	6.7 ± 4.1 (3.6—9.2)	50.9 ± 22.3 (29.3—69.4)	17.2 ± 22.0 (4.4—16.9)	<0.001
Sex, male	497 (54.2)	127 (44.4)	624 (51.9)	0.004
Influenza, type A	756 (82.4)	269 (94.1)	1025 (85.2)	<0.001
Underlying disease				
Chronic heart disease	33 (3.6)	44 (15.4)	77 (6.4)	<0.001
Chronic lung disease	153 (16.7)	46 (16.1)	199 (16.5)	0.856
Chronic kidney disease	8 (0.9)	27 (9.4)	35 (2.9)	<0.001
Liver cirrhosis	1 (0.1)	7 (2.4)	8 (0.7)	<0.001
Diabetes mellitus	1 (0.1)	54 (18.9)	55 (4.6)	<0.001
Immunosuppression	22 (2.4)	26 (9.1)	48 (4.0)	<0.001
Neurological disease	65 (7.1)	32 (11.2)	97 (8.1)	0.034
Laboratory findings				
Leukopenia	83 (9.2)	25 (8.7)	108 (9.1)	0.833
Thrombocytopenia	17 (1.9)	13 (4.8)	30 (2.6)	<0.001
Elevated CRP	388 (44.1)	221 (84.7)	609 (53.4)	<0.001
Complications				
Pneumonia	487 (53.1)	201 (70.3)	688 (57.2)	<0.001
ARDS	1 (0.1)	11 (3.8)	12 (1.0)	<0.001
Acute respiratory failure	5 (0.5)	27 (9.4)	32 (2.7)	<0.001
Septic shock	0 (0.0)	21 (7.3)	21 (1.7)	<0.001
Neurological complications	30 (3.3)	10 (3.5)	40 (3.3)	0.851
Cardiovascular complication	5 (0.5)	32 (11.2)	37 (3.1)	<0.001
Length of hospital stay (d)	4.2 ± 2.8 (3—5)	8.0 ± 12.2 (3—8)	5.1 ± 6.6 (3—5)	<0.001
Mortality	0 (0.0)	9 (3.1)	9 (0.7)	< 0.001
Bacteremia	4 (0.44)	10 (3.5)	14 (1.2)	<0.001
ECMO use	1 (0.1)	4 (1.4)	5 (0.4)	0.013
ICU stay	9 (1.0)	38 (13.3)	47 (3.9)	<0.001

[a] Leukopenia = WBC count < 4000/μL; thrombocytopenia = platelet count < 100 × 10^3/μL; elevated C-reactive protein (CRP) = CRP >1 mg/dL.
Data are presented as mean ± standard deviation with interquartile range (IQR) or n (%).
ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

had acute respiratory failure, septic shock, and acute renal failure on admission with blood culture positive for *S. pneumoniae* and later developed ventilator-associated pneumonia and multisystem organ failure (MSOF). Adults with bacteremia who died had a CRP range of 14.4—24.8 mg/dL, and an APACHE II score range of 23—35; and all had influenza A infection, pneumonia, septic shock, and acute respiratory failure. Blood cultures in all three patients positive for *A. baumannii* were carbapenem resistant, and all died. All adults with bacteremia were treated with antibiotics, and the majority of patients who died had inadequate initial empiric antibiotic treatment before the availability of blood culture results.

In the multivariate analysis, type B influenza, thrombocytopenia, and increased CRP were independently associated with bacteremia, as shown in Table 5. Because CRP was a significant predictor of bacteremia by multivariate analysis, receiver operating characteristic (ROC) analyses were performed for CRP, and CRP ≥ 14 mg/dL had a sensitivity of 90.0% and a specificity of 88.0% (data not shown).

Discussion

Influenza infection in adults was associated with an increased risk of pneumonia, ARDS, acute respiratory failure, septic shock, and cardiovascular complications compared with children in our study. The mortality for adults with influenza was 3.1%, and no child died of influenza infection. Bacteremia was more common in adults than in children hospitalized for influenza infection (3.5% vs. 0.4%). Although the rate of bacteremia was low, there was an increase in septic shock (60.0% vs. 5.4%), acute respiratory failure (50.0% vs. 8.0%), cardiovascular complications (60.0% vs. 9.4%), and mortality (50.0% vs. 1.4%) in adults with bacteremia compared to the nonbacteremic group, underscoring the important role of bacteremia in influenza virus infection. Other studies have reported increased complications in influenza infection associated with bacterial coinfection. In patients with critical illness from the 2009 pandemic influenza A (pH1N1) virus infection, 24.2% had bacteremia, and patients with bacterial coinfection were more likely to present with shock, have a longer duration of ICU care, require mechanical ventilation, and have a higher mortality rate (31%).[6] Hospitalization for viral infection with or without bacterial coinfection has been shown to be associated with an increased risk of mortality, pneumonia, ARDS, respiratory failure, multisystem organ failure, and septic shock.[11]

In our study, the rate of bacteremia in children was low (0.4%). In children with pH1N1 infection, bacterial coinfection occurred in 1.3%.[12] The bacteria isolated most

Table 2 Comparison of children and adults hospitalized for influenza infection with and without bacteremia[a]

Variables	Children (n = 917)			Adults (n = 286)		
	No (n = 913)	Yes (n = 4)	p	No (n = 276)	Yes (n = 10)	p
Age (y)	6.7 ± 4.1 (3.6–9.2)	4.1 ± 1.4 (3.3–4.8)	0.199	50.3 ± 22.3 (29.0–69.4)	67.8 ± 13.5 (53.4–84.5)	0.014
Sex, male	493 (54.0)	4 (100.0)	0.129	122 (44.2)	5 (50.0)	0.755
Influenza, type A	752 (82.4)	4 (100.0)	> 0.99	262 (94.9)	7 (70.0)	0.016
Underlying disease						
Chronic heart disease	33 (3.6)	0 (0.0)	> 0.99	40 (14.5)	4 (40.0)	0.051
Chronic lung disease	153 (16.8)	0 (0.0)	> 0.99	44 (15.9)	2 (20.0)	0.666
Chronic kidney disease	8 (0.9)	0 (0.0)	> 0.99	24 (8.7)	3 (30.0)	0.058
Liver cirrhosis	1 (0.1)	0 (0.0)	> 0.99	4 (1.4)	3 (30.0)	0.001
Diabetes mellitus	1 (0.1)	0 (0.0)	> 0.99	50 (18.1)	4 (40.0)	0.098
Neuromuscular disease	65 (7.1)	0 (0.0)	> 0.99	31 (11.2)	1 (10.0)	> 0.99
Laboratory findings						
Leukocytosis	121 (13.4)	0 (0.0)	> 0.99	52 (18.8)	6 (60.0)	0.006
Thrombocytopenia	17 (1.9)	0 (0.0)	> 0.99	9 (3.4)	4 (44.4)	<0.001
CRP > 4 (mg/dL)	98 (11.2)	2 (66.7)	0.036	118 (47.0)	9 (90.0)	0.009
CRP (mg/dL)	2.0 ± 3.8 (0.3–2.1)	3.6 ± 2.0 (1.5–5.4)	0.447	6.1 ± 6.7 (1.5–7.5)	17.3 ± 7.9 (14.4–23.5)	<0.001
Complications						
Pneumonia	483 (52.9)	4 (100.0)	0.127	194 (70.3)	7 (70.0)	> 0.99
ARDS	1 (0.1)	0 (0.0)	> 0.99	10 (3.6)	1 (10.0)	0.329
Acute respiratory failure	5 (0.5)	0 (0.0)	> 0.99	22 (8.0)	5 (50.0)	0.001
Septic shock	0 (0.0)	0 (0.0)	NA	15 (5.4)	6 (60.0)	<0.001
Neurological complications	30 (3.3)	0 (0.0)	> 0.99	9 (3.3)	1 (10.0)	0.304
Cardiovascular complications	5 (0.5)	0 (0.0)	> 0.99	26 (9.4)	6 (60.0)	<0.001
Length of hospital stay (d)	4.2 ± 2.8 (3.0–5.0)	7.0 ± 3.4 (4.5–9.5)	0.046	7.8 ± 12.3 (3.0–8.0)	13.0 ± 8.3 (5.0–17.0)	0.188
Mortality	0 (0.0)	0 (0.0)	NA	4 (1.4)	5 (50.0)	<0.001
Heart failure	0 (0.0)	0 (0.0)	NA	13 (4.7)	2 (20.0)	0.091
ECMO	1 (0.1)	0 (0.0)	> 0.99	2 (0.7)	2 (20.0)	0.006
ICU stay	9 (1.0)	0 (0.0)	> 0.99	33 (12.0)	5 (50.0)	0.005

[a] Leukocytosis = WBC count >12,000/μL; thrombocytopenia = platelet count < 100 × 10³/μL.

Data are presented as mean ± standard deviation with interquartile range (IQR) or n (%).

ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; NA = not applicable.

Table 3 Clinical features, blood culture results, and outcome of children with influenza and bacteremia

Case no.	Age (y)	Sex	Risk factors	Blood culture organism	Complications	ICU stay	Infection source
1	6	M	none	*Roseomonas*	nil	nil	Bloodstream[a]
2	3	M	none	*S. pneumoniae*	nil	nil	Pneumonia
3	3	M	none	*S. viridans*	nil	nil	Oral ulcer
4	3	M	none	*S. pneumoniae*	nil	nil	Pneumonia

[a] No other identifiable infection source.
ICU = intensive care unit; *S. pneumoniae* = *Streptococcus pneumoniae*; *S. viridans* = *Streptococcus viridans*.

often in children with bacteremia in our study was *S. pneumoniae*. However, in critically ill children during the 2009—2010 influenza pandemic, approximately 5% of the patients had bacteremia within 72 hours of pediatric intensive care unit (PICU) admission, and *Staphylococcus aureus* was the most common bacteria identified.[13] The most common bacteria isolated in our adults with bacteremia were *A. baumannii* and *E. coli*, whereas in critically ill patients with 2009 pH1N1, *S. aureus* was the most common pathogen in bacteremia, followed by *S. pneumoniae*.[6] Antibiotic resistance was an important factor in adults with bacteremia. Multiresistant Enterobacteriaceae and carbapenem-resistant *A. baumannii* were among the bacteria isolated in most adults with bacteremia who died (80%; 4 of 5 patients). ESBLs and ampC β-lactamases (AmpCs) are among common plasmid-mediated β-lactamases rapidly spreading among Enterobacteriaceae and resulting in resistance to several β-lactam agents.[14,15] In *A. baumannii*, carbapenem resistance is due mostly to carbapenemases[16,17] or to synergistic effects between carbapenemases that hydrolyze carbapenems and decreased expression of certain penicillin-binding proteins or other outer membrane proteins.[18,19]

Overall, 95.1% of children in our study received oseltamivir treatment, including all patients with bacteremia. Varying rates of antiviral use have been reported in other studies, including 88.2% (5.8% antiviral started prior to PICU admission)[13] and 98.7%.[12] All adults in our study received antiviral treatment, which is higher than in other studies. In patients with pH1N1 infection, 7% received antiviral treatment for influenza prior to ICU admission, and almost all received antiviral agents while in the ICU[6] and 52% of adults with severe influenza received oseltamivir.[20] In Taiwan, Centers for Disease Control, Republic of China (R.O.C.) offers reimbursement for antiviral use for diagnosed influenza infection during the influenza season; those having influenza infection with other comorbidity and on self-payment. Early initiation of oseltamivir treatment has been shown to be beneficial in patients with influenza, with an increased risk of severe disease when treatment was started ≥5 days after illness onset.[21]

Table 4 Clinical features, blood culture results, and outcome in adults with influenza and bacteremia

Case no.	Age (y)	Sex	Risk factors	Blood culture organism	Complications	ICU stay	Mortality	Infection source
1	70	M	CVD, DM, ESRD	*Enterobacter cloacae*	Septic shock ARF	Yes	Yes	Bed sore
2	67	F	None	*E. coli*	Septic shock, Af	No	No	Urinary tract infection
3	68	M	CVD, COPD, DM, ESRD	*K. pneumoniae*	AE of COPD	No	No	Pneumonia
4	50	M	None	*A. baumannii*	Septic shock, ARF, ARDS, MSOF	Yes	Yes	Pneumonia
5	84	F	BA, CVD, CVA, ESRD, Liver cirrrhosis	*P. mendocina*	Acute asthma attack	No	No	Pneumonia
6	61	F	DM	*E.coli*		No	No	Urinary tract infection
7	52	M	Liver cirrhosis	*A. baumannii*	ARF, septic shock	Yes	Yes	Pneumonia
8	84	M	COPD, Liver cirrhosis	*Serratia marcescens*	ARF, septic shock, Af, liver failure	Yes	Yes	Biliary tract infection
			Cholangio-carcinoma	*A.baumannii*				Pneumonia
9	84	F	CVD, DM	*E. coli*		No	No	Urinary tract infection
10	53	F	None	*S. pneumoniae*	ARDS, ARF, septic shock, MSOF	Yes	Yes	Pneumonia

A. baumannii = *Acinetobacter baumannii*; AE of COPD = acute exacerbation of chronic obstructive pulmonary disease; Af = atrial fibrillation; ARDS = acute respiratory distress syndrome; ARF = acute respiratory failure, requiring ventilation; BA = bronchial asthma; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; CVD = chronic significant cardiovascular disease (excluding hypertension); DM = diabetes mellitus; *E. coli* = *Escherichia coli*; ESRD = end-stage renal disease, on regular hemodialysis; ICU = intensive care unit; *K. pneumoniae* = *Klebsiella pneumoniae*; MSOF = multisystem organ failure; *P. mendocina* = *Pseudomonas mendocina*; *S. pneumoniae* = *Streptococcus pneumoniae*.

Table 5 Multivariate logistic regression model of risk factors for bacteremia in adult patients with influenza infection

Parameter	OR	95% CI of OR	p
Age (y)	1.03	0.98–1.08	0.192
Influenza, type A vs. B	0.05	0.004–0.59	0.018
Liver cirrhosis	13.84	0.53–361.94	0.115
Leukocytosis ($> 12{,}000/\mu L$)	3.40	0.22–51.55	0.378
Thrombocytopenia ($< 100 \times 10^3/\mu L$)	39.65	2.44–645.24	0.010
CRP (mg/dL)	1.18	1.06–1.31	0.003

CI = confidence interval; CRP = C-reactive protein; OR = odds ratio.

In the bacteremic group, 75% of children and all adults received antibiotics. In other studies, antibacterial treatment was used in 92% of cases, and in 100% of fatal cases of adults hospitalized with severe influenza.[20] In children hospitalized for pH1N1infection, 80% received antibacterial agents.[12] The administration of inadequate antimicrobial treatment to critically ill patients with BSIs was shown to be associated with greater hospital mortality compared with adequate antimicrobial treatment of BSIs.[22] In addition to antiviral treatment, early empiric antibiotic use should be considered for hospitalized patients with severe influenza infection who are at an increased risk of bacterial lower respiratory tract infections and bacteremia.

Risk factors more common in adults than in children with influenza included chronic heart disease, chronic kidney disease, liver cirrhosis, diabetes mellitus, immunosuppression, and neurologic disease. However, older age and liver cirrhosis were the only risk factors that appeared more frequently in adults with bacteremia than in the non-bacteremic group, in this study. Heart disease, lung disease, diabetes mellitus, renal disease, rheumatologic disease, dementia, stroke, pregnancy, and immunosuppression are all risk factors for influenza complications.[4] In adults with blood cultures performed at the emergency department, older patients (≥ 60 years) and those with diabetes mellitus were found to have a higher risk of bacteremia.[23] Although influenza B was independently associated with bacteremia in adults, all those who died had influenza A virus infection.

More than 65% of cases of bacteremia are associated with thrombocytopenia. The mechanism underlying thrombocytopenia in the absence of disseminated intravascular coagulation may be related to the suppression of platelet production, increased platelet utilization, and immune phenomena.[24] CRP values in most acute viral infections are $< 2–4$ mg/dL. A value > 10 mg/dL is more likely to be associated with bacterial infection, although infections due to certain viruses can cause elevated CRP levels.[25] Other studies identified CRP as a risk factor for bacteremia.[23,26] In our study, thrombocytopenia and increased CRP levels were independently associated with bacteremia in adults with influenza infection, and could help clinicians to identify those at increased risk of bacteremia.

The highest incidences of influenza infection in our study were from August 2009 to December 2009, which coincided with the 2009 pandemic influenza A (H1N1) virus infection. Another high incidence occurred in December 2010, consistent with an increase in influenza infection during winter. For influenza, the highest seasonal rate was found to be in the winter and the lowest seasonal rate was in the summer, and widespread morbidity and mortality occur, not only through infection but via bacterial superinfection. Knowledge of seasonal variations in the incidence of sepsis and severe sepsis would have important implications for public health, hospital resource utilization, and clinical research.[27]

No child died of influenza infection in our study. Influenza-associated deaths are uncommon among children. Annual mean influenza-associated mortality rates for underlying pneumonia and influenza deaths in persons younger than 1 year and age 1–4 years were 0.3 and 0.2 deaths per 100 000 person-years, respectively; compared to 22.1 deaths per 100,000 person-years in persons 65 years or older, during the 1990s.[28] In children hospitalized for pH1N1 infection, the mortality rate was 2.6%[11] and 8.9% for critically ill children.[13]

There were some limitations in our study. Our study was retrospective. The incidence of influenza and bacteremia may be underestimated because some patients with influenza may have had negative rapid antigen tests and blood cultures. This was a single-center study, and further studies focusing on the role of bacteremia in influenza infection would provide more data.

In conclusion, influenza infection in adults is associated with an increased risk of complications, bacteremia, and mortality compared with children. Although the incidence of bacteremia in influenza infection is low; bacteremia in adults is associated with a significant increase in acute respiratory failure, septic shock, and mortality. Thrombocytopenia and elevated CRP levels were independent risk factors for concomitant bacteremia in adult patients with influenza infection.

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