MAJOR ARTICLE

Pulmonary Complications of Interpandemic Influenza A in Hospitalized Adults

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Background. To define the pulmonary complications of influenza during the current interpandemic period, we reviewed clinical, laboratory, and radiographic data from 193 adults (≥18 years old) (1999–2003) who were hospitalized with influenza A during 4 winters.

Results. The mean age was 75 years, 8% had documented bacterial infection, 15% required intensive care unit treatment, and 6% died. Chest radiograph (CXR) findings were classified as showing acute disease (AD; $n = 101$) or no AD (NAD; $n = 92$). Most CXR findings were subtle in nature. Subjects with AD were more likely to have ≥1 cardiac diagnosis (odds ratio [OR], 2.2 [95% confidence interval {CI}, 1.2–4.1]), to have rales on examination (OR, 1.9 [95% CI, 1.0–3.7]), to be symptomatic for >3 days (OR, 2.2 [95% CI, 1.2–4.1]), and to be less likely to wheeze (OR, 0.37 [95% CI, 0.20–0.70]). Total and neutralizing anti-influenza antibody titers were lower in patients with influenza than in respiratory syncytial virus–infected control subjects ($P < .05$), which suggests a protective effect of antibody. Interestingly, antibody titers did not differ between subjects with AD and those with NAD.

Conclusion. In the absence of significant antigenic shifts, previous exposure to influenza, including vaccinations, may play a role in reducing the severity of influenza-associated lower respiratory tract disease.

During previous influenza pandemics, many patients hospitalized with influenza had serious lower respiratory tract infections, including a rapidly progressive viral pneumonia with concomitant or secondary bacterial infections [1]. In an immune-naive population, pandemic influenza often causes high morbidity and mortality rates and impressive findings on chest radiographs (CXRs) [1]. During the present interpandemic period, influenza continues to be an important cause of hospitalizations and mortality [2, 3], despite the advent of antivirals and vaccines for prophylaxis and treatment [4, 5].

There have been limited clinical descriptions of nonpandemic influenza involving the lower respiratory tract [6–10]. Approximately 25% of patients hospitalized with influenza have CXR findings consistent with pneumonia [7–10]. However, such radiographic findings have not been described in detail, nor have they been correlated with clinical or laboratory parameters. Furthermore, new sensitive diagnostic tests, such as reverse-transcription polymerase chain reaction (RT-PCR), may identify a different spectrum of disease than previously described. Thus, we sought to characterize the pulmonary complications of influenza in hospitalized adults during the present interpandemic period.

SUBJECTS, MATERIALS, AND METHODS

Subjects

During 4 consecutive winters (15 November–15 April) from 1999 to 2003, we identified patients who met the following criteria: (1) age ≥18 years; (2) documented influenza A virus infection (see illness definition, below); (3) ≥1 CXR obtained within 72 h of hospital admission; (4) influenza A deemed not to be nosocomial; and (5) hospitalized at Rochester General Hospital

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(RGH), a 524-bed community teaching hospital in Rochester, New York.

During the study period, inpatients were actively screened for influenza through the hospital infection-control program. At the start of each winter season, all patients admitted with acute cardiopulmonary diagnoses (regardless of the presence or absence of fever) were screened by viral culture. Swabs of each naris and throat (NPS) were combined into a single tube of viral transport medium. Once influenza was identified by viral culture, rapid influenza A antigen test and viral culture (if the antigen test was negative) was performed on all patients subsequently hospitalized with acute cardiopulmonary conditions. The majority of screening for influenza was performed in the emergency department. Approximately 11% of patients screened were found to have influenza [11].

A subset of inpatients ($n = 140$) with influenza participated in a prospective study of respiratory illness and had RT-PCR and acute and convalescent serologic testing performed in addition to viral culture and antigen testing [11]. Enrolled subjects were interviewed and examined at enrollment. For subjects who did not participate in the prospective study and who were identified by infection-control records ($n = 53$), data collection was limited to retrospective chart review. For each patient, clinical, laboratory, and radiographic data were recorded. Nursing assessments of functional abilities were used to calculate the Katz Activities of Daily Living (ADL) score, an indicator of functional status [12]. The study was approved by the institutional review boards of the RGH and the University of Rochester School of Medicine and Dentistry.

Laboratory Methods

Bacterial cultures. Bacterial cultures of blood and sputum and sputum Gram's stains were performed by the RGH clinical microbiology laboratory using standard procedures.

Rapid antigen test. The presence of influenza A antigen was determined using the Directigen kit (BD Biosciences).

Viral cultures. NPS samples were inoculated onto rhesus monkey cells and examined daily for cytopathic effect; hemadsorption was performed on day 10. Viral growth was confirmed with virus-specific monoclonal antibodies (Bartels).

RT-PCR. A single-tube nested RT-PCR assay was performed on frozen aliquots of NPS samples [13]. Oligonucleotides complementary to a conserved sequence of the influenza A M gene were used [11]. The sensitivity of the assay is 0.1 pfu [14].

EIA. Serum IgG titers against influenza A virus were measured in duplicate by EIA [15]. For each study year, antigens were prepared from the predominant circulating H3N2 strain.

Microneutralization assay (MNA). Titers of serum neutralizing antibodies against influenza were measured using a modified MNA [16]. MDCK cells were plated in 96-well microtiter plates to reach 80%–90% confluence by the following day. Serial 2-fold serum dilutions (starting at 1:25) in modified Eagle medium (MEM) with 500 μg/mL trypsin and 0.1% gelatin were mixed with ~75 pfu of the appropriate strain of influenza virus. After incubation at room temperature for 45 min, the serum plus virus dilutions were added in duplicate to the MDCK cell monolayers that were prewashed twice with PBS and once with MEM/trypsin/gelatin. After incubation for 48 h

Table 1. Demographics of the study population.

Characteristic	Value ($n = 193$)
Age, mean ± SD, years	75 ± 14
Female sex	106 (55)
Ethnicity	
White	166 (86)
Black	17 (9)
Hispanic	9 (5)
Any cardiac disease	107 (55)
Any lung disease	100 (52)
Any heart or lung disease	157 (81)
Immunosuppression	
Diabetes mellitus	45 (23)
Cancer	22 (11)
Leukemia/lymphoma	1 (<1)
Long-term oral steroids	13 (7)
Inhaled steroids	32 (17)
Pregnancy	1 (<1)
HIV/AIDS	0
Residence in a long-term-care facility	26 (13)
Smoking[a]	
Current	38 (21)
Former	85 (48)
Never	54 (31)
Influenza vaccine[a]	103 (76)
Katz ADL score, mean ± SD	2.1 ± 3.5

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Cardiopulmonary diagnoses were listed using the standard numerical coding for the Program of All-Inclusive Care for the Elderly [27]. Respiratory diseases included bronchospasm (asthma), bronchitis, pneumonia, pleural effusion, pulmonary embolus, chronic obstructive pulmonary disease, tuberculosis, emphysema, pneumothorax, pleurisy, and other respiratory disease (i.e., not described in any other listed above). Each patient record was screened for the presence of the following cardiovascular diagnoses: myocardial infarction, congestive heart failure, valvular heart disease, rheumatic heart disease, arteriosclerotic heart disease, hypertensive cardiovascular disease, cardiomyopathy, hypertension, malignant hypertension, atrial fibrillation, ventricular arrhythmia, heart block (first, second, and complete), permanent or temporary pacemaker, cardiopulmonary arrest, pericarditis, peripheral vascular disease, and other cardiovascular disease (i.e., not described in any other listed above). ADL, Activities of Daily Living test.

[a] History of smoking and influenza vaccination status could not be ascertained for all subjects; there were data from 177 for smoking and from 136 for influenza vaccination.

Table 2. Chest radiograph classifications and documented bacterial infections/virologic diagnosis.

Classification	Acute disease (n = 101)	No acute disease (n = 92)
Documented bacterial infections		
Infiltrates (n = 33)	Sputum, *Moraxella catarrhalis* (1), GNR (1); blood, *Streptococcus pneumoniae* (1)	Sputum, *Haemophilus influenza* (1), *Staphylococcus aureus* (3), *M. catarrhalis* (2), *S. pneumoniae* (1), GNR (2); blood, *S. aureus* (1)
Atelectasis vs. infiltrates (n = 45)	Sputum, *S. pneumoniae* (2), GNR (1)	
Congestion/edema vs. infiltrates (n = 7)	No concomitant bacterial infections	
Edema (n = 16)	Sputum, *S. aureus* (1), GNR (1)	
Total	Sputum, 7; blood, 1	Sputum, 9; blood, 1
Diagnosis of influenza, no. (%)		
Rapid antigen and/or culture positive	56 (55)	51 (55)
RT-PCR positive; culture/rapid antigen negative	35 (35)	26 (28)
Serologically positive only	10 (10)	15 (16)

NOTE. GNR, gram-negative rods; RT-PCR, reverse-transcription polymerase chain reaction.

at 37°C, the quantity of influenza antigen was determined by EIA using a monoclonal antibody against influenza A (catalog number B1029-87B; Bartels) [15]. The neutralization titer was defined as the $\log_2$ titer of the serum dilution resulting in a 50% reduction in color development.

Serum and viral strains used for immunologic analysis. To control for inter- and intraassay variation in EIAs and MNAs, well-characterized control serum that provided high and low assay values was included in every assay. Influenza A viruses used as the infecting virus in the neutralization assay and as source of viral antigen for EIA were as follows (on the basis of sequence analysis of the hemagglutinin gene): 1999–2000 season, H3N2 (98% homology to A/Swine Colorado/99), and 2001–2002 season, H3N2 (96% homology to A/Swine Colorado/99).

Patient Methods

Illness definitions. Influenza virus infection was defined as an illness with a positive viral culture, rapid antigen, RT-PCR, or diagnostic serologic testing. A ⩾4-fold increase in antibody titer ⩾4 weeks after an illness was considered to be positive. For illnesses that occurred within 4 weeks after influenza vaccination, the antibody response alone was insufficient to define influenza virus infection. Bacterial infections were defined as illnesses associated with blood cultures positive for bacteria other than coagulase-negative staphylococci or a sputum culture showing 3+ or 4+ growth of a potential pathogen from an adequate sample (>10 white blood cells, <10 epithelial cells/low-power field).

Immunologic analysis. To determine whether serum antibody titers correlated with influenza hospitalization and CXR findings, influenza antibody titers in serum samples from patients with acute influenza were measured by EIA and MNA in a subset of patients from whom blood was available. Because the majority of influenza cases occurred in 1999–2000 and 2001–2002, when the predominant viral strain was H3N2, serum was used from 119 subjects who were hospitalized during these years. Influenza antibody titers were also measured in 60 control subjects hospitalized during the same 2 years who had

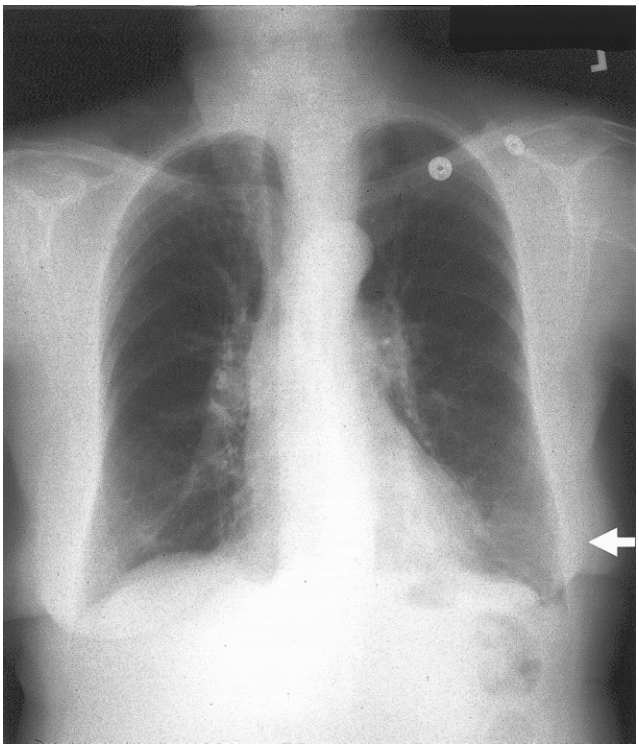

Figure 1. Representative chest radiograph from a study subject. The arrow indicates the location of the radiographic findings. The official reading was left basilar atelectasis vs. pneumonia in an 82-year-old male with steroid-dependent asthma, hypertension, and atrial fibrillation. Influenza was diagnosed by serologic testing.

Table 3. Chest radiograph classifications and demographic and clinical characteristics.

Characteristic	Acute disease (n = 101)	No acute disease (n = 92)	Statistical result
			P
Univariate analysis			
Influenza vaccination	51/67 (76)	52/69 (75)	NS
Any cardiac disease	63/101 (62)	44/92 (48)	.04[a]
Any lung disease	51/101 (50)	49/92 (53)	NS
COPD	39/101 (39)	40/92 (43)	NS
Enrollment Katz score, mean ± SD	2.7 ± 3.9	1.5 ± 2.9	.01[a]
Days of symptoms before admission, mean ± SD	5.4 ± 5.0	4.4 ± 6.7	.03[b]
Symptoms for >3 days before admission	50/98 (51)	32/91 (35)	.04[a]
Wheezing on examination	51/100 (51)	63/92 (68)	.02[a]
Rales on examination	59/98 (60)	45/92 (49)	.14
			OR (95% CI)
Multivariate analysis			
Any cardiac disease	63	48	2.2 (1.2–4.1)
Symptomatic for >3 days	51	35	2.2 (1.2–4.1)
Rales on examination	60	49	1.9 (1.0–3.7)
Wheezing on examination	51	68	0.37 (0.20–0.70)

NOTE. Data are no. with characteristic/total (%) or percentage of subjects, unless otherwise indicated. For the multivariate logistic regression analysis, $P < .05$ for all variables listed above. CI, confidence interval; COPD, chronic obstructive pulmonary disease; NS, not significant; OR, odds ratio.

[a] Fisher's 2-sided exact test.

[b] Wilcoxon 2-sided rank sum test.

documented respiratory syncytial virus (RSV) infection. Samples from RSV- and influenza virus–infected patients were run concurrently and were anonymously coded with regard to infection status. Antibody titers in influenza virus–infected subjects with acute disease (AD) on CXRs were compared with those with no acute disease (NAD), and subjects vaccinated against influenza were compared with those who were not.

Classification of CXRs

For each patient, official radiologist readings of CXRs obtained within 72 h of hospital admission were recorded. For patients with ⩾1 set of CXRs, the most severe reading was used to determine the final classification.

CXRs were classified into 1 of 2 groups. The first group (AD) consisted of those with new radiographic findings consistent with AD. Such readings described (1) infiltrates/air-space opacities consistent with pneumonia, (2) less well defined opacities consistent with atelectasis or either infiltrates or atelectasis, (3) vascular congestion/edema versus infiltrates, or (4) edema. The lobar and/or sublobar locations of radiographic findings were also recorded. The second group (NAD) consisted of films read as normal or showing NAD.

Statistical Analyses

Statistical manipulations were performed using JMP (version 5.1.2; SAS). For univariate analyses, means were compared with Wilcoxon rank sum tests, and proportions were compared using 2-tailed Fisher's exact tests. For multivariate analyses, logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

Patient Population

A total of 193 patients with documented influenza A infection during 4 consecutive winter seasons (1999–2003) met the inclusion criteria. During the 4 winters, the predominant circulating strains of influenza virus in the mid-Atlantic region were as follows: 1999–2000, 99.5% influenza A H3N2; 2000–2001, 63% influenza B and 37% influenza A (97% H1N1); 2001–2002, 88% influenza A (98% H3N2) and 12% influenza B; and 2002–2003, 86% influenza A (70% H1N1) and 14% influenza B [11]. The majority of subjects (169/193; 88%) had influenza during the first and the third seasons, when H3N2 viruses predominated.

Demographics of the study population are summarized in table 1. The mean age of the subjects was 75 years. There were 30 (15%) subjects who were <65 years old. Of the 6 (3%) who were <40 years old, 4 had a history of asthma. There was a slight preponderance of women (55%), and most subjects were white (86%). At the time of hospitalization, 191 (99%) had ⩾1 underlying medical diagnosis. The majority of subjects (81%) had underlying cardiovascular or pulmonary disease,

Table 4. Hospitalization course and outcomes.

Outcome	Acute disease (n = 101)	No acute disease (n = 92)
Treatment		
Steroids	47/101 (47)	56/91 (62)[a]
Antibiotics	89/101 (88)	82/92 (89)
Antivirals	36/101 (36)	34/91 (37)
Complications		
ICU admission	16 (16)	12 (13)
Mechanical ventilation	10 (10)	11 (12)
Hospital days, mean ± SD	8.6 ± 5.1	8.9 ± 10
Deaths	6 (6)	5 (5)
Deaths from respiratory failure	2 (2)	2 (2)

NOTE. For treatment options, data are no treated/total. Other data are no. (%) of subjects, unless otherwise indicated. ICU, intensive care unit.

[a] $P < .05$, Fisher's 2-sided exact test.

and 23% had a previous diagnosis of congestive heart failure (CHF). Only 2 subjects (1%) had a history of rheumatic heart disease. Some patients were considered to have immunosuppression because of underlying diabetes mellitus (23%), cancer (11%), long-term oral (7%) or inhaled (17%) steroid use, or pregnancy (<1%). No patient had a documented history of HIV/AIDS. At the time of hospitalization, a minority of subjects (13%) resided at a long-term-care facility. Most subjects (123/177 [69%]) for whom a smoking history was elicited were either current or former smokers. The annual vaccination status for influenza was clearly documented in 136 subjects, of whom 103 (76%) had received the vaccine. Subjects were moderately frail, with a mean ± SD Katz ADL score of 2.1 ± 3.5. In general, the frequencies of major underlying diagnoses in our study population were similar to those previously identified among community-dwelling elderly persons [17, 18].

Radiographic findings. Subjects were classified according to the official readings of admission CXRs (table 2). In all, radiographic findings from 101 patients were classified as AD, and those from 92 subjects were categorized as NAD.

In the AD group, the most common radiographic finding (45/101 [45%]) was atelectasis versus infiltrates that involved the lung bases and/or lower lobes in a unilateral (left, 22 patients; right, 8 patients) or bilateral (9 patients) distribution. A representative CXR from this group is shown in figure 1. CXRs from 33 subjects (33%) had pneumonic infiltrates, most commonly noted in the left lower lobe (11 patients). Of the remaining subjects, 16 (16%) bore radiographic changes consistent with edema, and 7 (7%) had findings read as congestion/edema versus infiltrates.

By contrast, CXR readings of patients in the NAD group were almost equally divided between "normal" (43 patients [47%]) or NAD (49 patients [53%]). Films from 20 subjects (22%) bore underlying radiographic findings without associated acute changes. Such findings included emphysema (7 patients), scarring (3 patients), mass lesions (2 patients), prior right lobectomy (1 patients), and cardiomegaly without radiographic evidence of CHF (7 patients).

Concomitant bacterial infections. In all, 18 (9%) of 193 subjects had positive blood or sputum cultures (table 2). Sputum cultures were collected within 48 h of admission in 43 (22%) of 193 subjects in the study. A total of 16 sputum samples, each obtained from a single patient (i.e., 39% of sputum samples), were deemed to be adequate and grew the following pathogens: *Streptococcus pneumoniae,* 3; *Haemophilus influenzae,* 1; *Staphylococcus aureus,* 4; *Moraxella catarrhalis,* 3; and gram-negative rods, 5. Nine subjects in the NAD group and 7 in the AD group had positive bacterial culture results from their respective sputum samples. Blood cultures were obtained within 48 h of admission from 114 (59%) of 193 subjects, and only 2 were positive *(S. pneumoniae* and *S. aureus).*

The majority (55%) of both radiographic classification groups were culture and/or rapid antigen test positive for influenza (table 2). In each group, a smaller percentage of subjects were diagnosed by RT-PCR with negative viral cultures (AD, 35%; NAD, 28%) and by serologic testing only (AD, 10%; NAD, 16%). The minor differences between the 2 groups with respect to diagnostic measures were not statistically significant.

Demographics, clinical presentation, and laboratory diagnosis of influenza A. The demographics, clinical presentation, and laboratory parameters were compared for those with and without radiographic findings of AD by use of univariate and multivariate analyses (table 3). Notably, the radiographic characterization was unrelated to vaccination status (AD, 76%; NAD, 75%) or the presence of underlying lung disease or chronic obstructive pulmonary disease (table 3). However, 2 baseline characteristics were statistically different between groups. Those with AD on CXRs were more likely to have ⩾1 underlying cardiac diagnosis (63% for AD vs. 48% for NAD; $P = .04$), whereas those with NAD on chest radiographs were more frail, as evidenced by higher Katz ADL scores at admission (2.7 ± 3.9 for NAD vs. 1.5 ± 2.9 for AD; $P = .01$).

Between the 2 groups, there were no differences with respect to home medications (chronic oral or inhaled steroid use, bronchodilators, and home oxygen) or clinical symptoms (data not shown). However, subjects with AD radiographic findings were symptomatic ~1 day longer than those with NAD CXRs (mean ± SD, 5.4 ± 5.0 days for AD vs. 4.4 ± 6.7 days for NAD; $P = .03$), more likely to be symptomatic for >3 days (51% vs. 35%, respectively; $P = .04$), and showed a trend toward an increased incidence of rales on examination (60% vs. 49%, respectively; $P = .14$). By contrast, more subjects with NAD on CXRs had wheezing than did subjects with AD (68% vs. 51%, respectively; $P = .02$).

Using multivariate logistic regression, each of these 4 dif-

Table 5. Deaths among study participants.

Age/sex	Underlying medical conditions	Complications during hospital stay	Ventilation	CXR	Cause of death and hospital day
71/F	Severe COPD	Respiratory failure	Yes	NAD	Respiratory failure on day 7
81/M	CAD, CHF, DM	MI, renal failure, respiratory failure	Yes	Edema	Cardiogenic shock on day 9
94/F	CAD, DM, HTN	Rapid Afib, cardiopulmonary arrest after 1 day of improvement	Yes	Bilateral infiltrates-edema vs. pneumonia	Cardiopulmonary arrest on day 3
94/F	Dementia, HTN	Respiratory failure	No	RUL Infiltrate	Respiratory failure, pneumonia on day 6
69/F	Severe COPD, HTN, steroid myopathy	Abdominal pain acidosis	Yes	NAD	Abdominal catastrophe on day 22
82/F	Severe COPD	Visceral perforation	No	Atelectasis	Visceral perforation on day 37
87/F	COPD	Rapid Afib, diarrhea, line infection, UTI, respiratory failure	Yes	NAD	Mutifactorial on day 26
83/M	Dementia, CAD, PVD	Respiratory failure, *Torulopsis* fungemia	Yes	RUL infiltrate	Fungal sepsis, pneumonia on day 6
68/M	Metastatic lung CA, CAD, COPD	Respiratory failure, ORSA bronchitis	Yes	Multiple nodules consistent with metastatic disease	Respiratory failure on day 11
70/F	COPD, ESRD on HD, Afib	Pancreatitis, hypotension, ischemic bowel, respiratory failure	Yes	RLL atelectasis vs. pneumonia	Metabolic acidosis, respiratory failure on day 26
82/M	Asthma, DM, CAD, CHF	Respiratory distress	No	Right lung base atelectasis vs. pneumonia	Cardiopulmonary arrest on day 4

NOTE. Afib, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CXR, chest radiograph; DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; HD, hemodialysis; HTN, hypertension; M, male; MI, myocardial infarction; NAD, no acute disease; ORSA, oxacillin-resistant *Staphylococcus aureus;* PVD, peripheral vascular disease; RLL, right lower lobe; RUL, right upper lobe; UTI, urinary tract infection.

ferences remained independent and statistically significant ($P < .05$). Compared with subjects with NAD CXR findings, those with AD findings were more likely to have ⩾1 cardiac diagnosis (OR, 2.2; [95% CI, 1.2–4.1]), to have rales on examination (OR, 1.9 [95% CI, 1.0–3.7]), to be symptomatic for >3 days (OR, 2.2 [95% CI, 1.2–4.1]), and to be less likely to wheeze (OR, 0.37 [95% CI, 0.20–0.70]). A subanalysis of the 33 subjects in the AD group with pneumonia (i.e., those with definite air-space opacities read as infiltrates), compared with the 92 subjects in the NAD group, yielded similar trends, and 3 variables (days of symptoms before admission, the proportion of patients symptomatic for >3 days before admission, and wheezing on examination) remained statistically significant ($P < .05$).

Hospitalization Outcomes

The relationships between radiographic classifications and hospitalization course were examined (table 4). The majority of subjects in both groups were treated with antibiotics, whereas approximately one-third of each group received antivirals. Significantly more subjects with NAD radiographic findings were treated with steroids, compared with the AD group (62% vs. 47%, respectively; $P < .05$).

The following antivirals were used: amantadine (19 patients), rimantidine (34 patients), zanamivir (1 patient), and oseltamivir (14 patients). One subject received both rimantidine and oseltamivir. The use of antivirals did not significantly affect the death rate, length of stay in the intensive care unit (ICU), or duration of hospitalization. In all, 13 (19%) of 70 of subjects who received antivirals required mechanical ventilation, compared with 8 (7%) of 122 of those who did not receive antivirals ($P = .015$), which suggests that physicians were more likely to treat more severely ill patients.

In each group, similar proportions of subjects were transferred to the ICU (AD, 16%; NAD, 13%) and underwent mechanical ventilation (AD, 10%; NAD, 12%). A small number of subjects experienced additional complications, including myocardial infarction (6 for AD vs. 3 for NAD), cerebrovascular accident (2 for AD vs. 0 for NAD), and nosocomial pneumonia (1 for AD vs. 3 for NAD). The 2 groups did not significantly differ with respect to the mean number of days of hospitalization. In all, 11 (6%) of 193 patients with influenza A died, of whom 6 had CXRs classified as AD and 5 as NAD (table 5). All 11 subjects who died were elderly and had underlying cardiac and/or pulmonary disease. Eight subjects required ICU care and mechanical ventilation. Four died of respiratory failure, and death followed withdrawal of care in 9 patients.

Influenza humoral immunity. Patients hospitalized with influenza A ($n = 119$) had lower mean EIA titers of anti-influenza antibodies than those admitted with RSV ($n = 60$) (mean ± SD $\log_2$ serum dilution, 14.69 ± 1.37 for influenza vs. 15.22 ± 1.49 for RSV; $P < .01$) (table 6). Similar results were obtained when MNA titers (expressed as $\log_2$ dilution against influenza) were examined (for influenza virus–infected subjects, 7.89 ± 1.62; for RSV-infected control subjects, 8.80 ± 1.81; $P < .01$). There were no significant differences between groups in the proportion of subjects vaccinated against influenza (table 6).

Among the influenza virus–infected patients, there were no significant differences in EIA or MNA titers between subjects with AD on CXR ($n = 62$) and those with NAD ($n = 55$), nor was there a difference between vaccinated ($n = 83$) and nonvaccinated ($n = 20$) subjects (table 6). Similar results were noted when titers from patients with documented radiographic infiltrates ($n = 20$) were compared with those from the NAD group ($n = 55$) (data not shown).

DISCUSSION

To our knowledge, this is the largest review of pulmonary complications of influenza A in hospitalized adults during the present interpandemic period. Because our results are based on the demographics of patients at a large community hospital and the use of sensitive diagnostic assays, they are likely to reflect the current spectrum of clinical and radiographic manifestations of influenza among hospitalized adults with documented influenza virus infection.

Our patient population was predominantly composed of el-

Table 6. Immunological response against influenza A in respiratory syncytial virus (RSV)–infected control subjects vs. those with influenza A.

Test	RSV control ($n = 60$)	Influenza A ($n = 119$)	P
EIA	15.2 ± 1.5	14.7 ± 1.4	.0055
MNA	8.8 ± 1.8	7.9 ± 1.6	.0016
	Influenza A, AD ($n = 62$)	Influenza A, NAD ($n = 55$)	
EIA	14.8 ± 1.5	14.6 ± 1.3	NS
MNA	8.0 ± 1.6	7.8 ± 1.6	NS
	Influenza A vaccinated ($n = 83$)	Not vaccinated for influenza A ($n = 20$)	
EIA	14.7 ± 1.2	15.1 ± 1.4	NS
MNA	7.8 ± 0.2	8.1 ± 0.3	NS

NOTE Data are mean ± SD $\log_2$ titers. For the RSV-infected control subjects, 50 had been vaccinated for influenza A, 5 had not been vaccinated, and 5 had unknown vaccination status. For influenza A virus–infected subjects, 83 had been vaccinated for influenza A, 20 had not been vaccinated, and 16 had unknown vaccination status. Wilcoxon's 2-sided rank sum test was used for most comparisons. In the first comparison, vaccinated subjects were compared using Fisher's 2-sided exact test, and the proportion of subjects in each group that were vaccinated against influenza was not significantly different ($P = .11$ if subjects with unknown vaccination status were excluded; $P = .07$ if such subjects were classified). AD, acute disease; MNA, microneutralization assay; NAD, no acute disease; NS, not significant ($P > .05$).

derly adults with a high incidence of underlying cardiopulmonary conditions. On the basis of available culture results, the minimum rate of documented bacterial infections was 8%. During hospitalization, the mortality rate was 6%, which was similar to that for RSV-infected hospitalized adults (8%) [11]. These clinical observations are significantly different from those of the 1918–1919 and 1957–1958 influenza pandemics, in which relatively young adults, many of whom had a history of rheumatic heart disease and/or were immunologically naive to pandemic influenza virus strains, presented with acute respiratory distress, hypoxia, and cyanosis and had high rates of concomitant bacterial infections and death [1, 19–22].

During the present interpandemic period, retrospective population-based studies have shown that annual seasonal epidemics of influenza in children and adults are associated with increased influenza-associated hospitalizations and mortality [2, 3]. On average, influenza was associated with 3 times as many deaths as RSV [3]. Our findings may differ from those of previous studies, in part because of our highly vaccinated population, which may have reduced severe disease. Furthermore, because inclusion in our study required a specific viral diagnosis, we may have missed patients with influenza who suddenly died or were hospitalized with a cardiopulmonary event that was triggered by a recent influenza virus infection.

In contrast to the diffuse air-space opacities seen on CXRs during pandemics, most radiographs in the present study showed remarkably subtle findings without clear evidence of lower respiratory tract disease. Only a limited number of clinical parameters were associated with the presence of acute radiographic findings, some of which were read as edema and were thus consistent with the high incidence of cardiovascular disease in this group. Subjects without new radiographic findings had an increased incidence of wheezing and were more frequently treated with steroids, which suggests that reactive airway disease due to upper or lower respiratory tract infection led to hospitalization in these patients.

Given their ages, the subjects in the present study have likely been exposed to multiple H1N1, H2N2, and H3N2 influenza virus strains and to have received multiple influenza vaccinations during their lifetimes. Such immunological exposures likely diminished the incidence of serious pulmonary complications of influenza. Consistent with this idea, adults who had symptomatic influenza A during earlier study years of the Cleveland Family Study were less susceptible to the H2N2 influenza virus causing the 1957–1958 pandemic, compared with adults who were previously uninfected [23, 24].

Our finding that influenza virus–infected subjects had lower influenza antibody titers than RSV-infected control subjects suggests that influenza antibody is protective against serious illness requiring hospitalization. The level of exposure to influenza virus among the RSV-infected control subjects is unknown, and the titers of influenza virus–infected subjects may have begun to increase at the time of hospitalization; these factors would reduce the differences in antibody titer between the 2 groups. Despite these issues, our observation of a modest but statistically significant difference suggests that the differences in antibody titer are meaningful. An inverse correlation of anti-hemagglutinin or -neuraminidase antibody levels to the risk of influenza illness in nursing-home outbreaks or in experimental human challenges with the H3N2 strain has been reported [25, 26]. However, we are unaware of reports describing the serum anti-influenza antibody levels in patients hospitalized with influenza.

Despite the association of lower antibody titers and hospitalization, we did not find a similar association with radiographically apparent lower respiratory tract disease or with vaccination status. Thus, the radiographic findings in our study may be more indicative of underlying comorbidities of the patient population than the extent of viral invasion of the lower respiratory tract. The relationship between vaccination and serum antibody titers requires further study. In the absence of significant antigenic shifts, such as those seen in pandemics, previous exposure to influenza, including vaccinations, may play a role in reducing the severity of influenza-associated lower respiratory tract disease

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