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Influenza pneumonia: a comparison between seasonal influenza virus and H1N1 pandemic.

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ABSTRACT

Objective

We compared clinical presentation, complications as well as the outcome in patients with influenza A(H1N1) and seasonal influenza pneumonia.

Methods

The group of patients with influenza A(H1N1) pneumonia consisted of 75 patients. Fifty two patients with pneumonia associated with seasonal influenza were included for comparison.

Results

Patients with pneumonia associated with novel H1N1 influenza were younger (mean 39.7 versus 69.6 years) and had less chronic comorbidities and alcoholism. Infiltrates were more extensive and frequently interstitial. Respiratory failure was more frequent (PaO_2/F_IO_2 < 200 28 versus 12%, p=0.042), leading to a higher rate of intensive care unit admission and mechanical ventilation (29.3 versus 7.7%, p<0.0030 and 18.7 versus 2%, p<0.0045). Mortality was double as high in patients with novel H1N1 (12% versus 5.8%, p=0.238) even not significantly, and was attributable to pneumonia in most instances (77.8% versus 0, p=0.046).

Conclusions

Younger age, less comorbidity, more extensive radiographic extension and more severe respiratory compromise and intensive care unit admission are key features of clinical presentation of patients with novel H1N1 associated pneumonia compared to seasonal influenza pneumonia

Keywords: Influenza A (H1N1) pneumonia, Community acquired pneumonia, Seasonal influenza pneumonia, viral pneumonia

INTRODUCTION

Studies assessing the aetiology of community-acquired pneumonia unanimously have shown influenza virus to be a frequent pathogen involved. The reported frequencies vary between 4 and 19% [1].

Seasonal influenza virus infection has been shown to be associated with considerable excess mortality, particularly in elderly and comorbid patients, at least in seasons with high influenza activity. Recently, from the 1976/1977 through the 2002/2003 seasons an annual average of more than 25,000 influenza-associated respiratory and circulatory deaths (9.9 deaths per 100,000) have been calculated in the United States, mostly affecting the younger (< 5 years age) and the elderly (> 50 years of age) [2].

The pandemics in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2) were PubMed characterised by major excess morbidity and mortality as a consequence of viral reassortment. For the same reason the novel influenza A (H1N1) virus was suspected to be highly pathogenic since its rapid spread in Mexico in 2009. Therefore, the emergence of novel H1N1 influenza in 2009 has been a major challenge for public health and medical institutions and, a global pandemic was declared in July 2009.

Early during this recent pandemic, it has become evident that there are consistent differences in host characteristics, clinical presentation and outcomes between patients with novel H1N1 and seasonal influenza virus [3, 4]. We, therefore, compared these features in large populations presenting with seasonal and novel H1N1 influenza virus associated pneumonia.

METHODS

Inclusion criteria and definitions

The study was approved by local Ethics Commitees, Ref. 2009/5251.

Immunocompetent patients aged >16 years and confirmed influenza virus infection as well as community-acquired pneumonia were included in the analysis.

Immunocompetence was defined in the absence of neutropenia, solid organ or stem cell transplantation, HIV-infection, and any immunosuppressive treatment, including oral steroid treatment at daily dosages of > 15mg.

Community-acquired pneumonia was diagnosed in the presence of a new infiltrate on chest radiography together with symptoms of lower respiratory tract infection as well as the absence of alternative diagnoses at follow-up. Pneumonia was classified as reason for hospitalization in the absence of other evident reasons, e.g. decompensated comorbidity. Bacterial pneumonia cases were excluded. Death was attributed to pneumonia clinically in the absence of other lethal complications.

Patient populations

Overall, 52 patients with pneumonia associated with seasonal influenza were included. Of these, 42 were consecutively diagnosed and admitted between October 2003 and December 2008 at the Hospital Clinic in Barcelona, Spain; 10 corresponded to patients hospitalized at the Hospital de Puerto Montt, Chile between April 2005 and March 2006. Diagnosis of seasonal influenza was established by seroconvertion, i.e. fourfold increase of IgG in the complement fixation test (Barcelona) and in the hemagglutination test (Puerto Montt).

The group of patients with novel H1N1 group associated pneumonia consisted of 75 patients admitted during May and July 2009 in Puerto Montt. These patients were diagnosed by PCR.

Microbiological investigations

Patients with seasonal influenza were part of a prospective etiological study including blood cultures, sputum, antigen-testing for *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* as well as serology in both settings. Patients with H1N1were investigated according to the decision of the attending physicians.

Data

The following parameters were recorded at admission: age, sex, comorbidity, smoking and alcohol habits, previous antibiotic therapy in the last month before the flu episode, symptoms (fever, chills, cough, sputum, chest pain) and findings (crackles). Pneumonia severity was assessed by PSI [5] and CRB-65 scores [6, 7]. CURB-65 was not available for all patients (blood urea value) due to situation of healthcare emergency (H1N1 pandemic), that obliged to a rapid decision-making-process in the emergency department for patients' evaluation. Radiographic patterns were classified as alveolar, interstitial or mixed, and the presence of pleural effusion was assessed. Moreover, all patients were assessed at admission and daily during follow-up for the presence of confusion, hypotension (systolic blood pressure < 90mmHg), renal failure, bilateral infiltrates, septic shock, ICU admission and mechanical ventilation administration.

Statistics

Categorical variables were described by frequencies and percentages, while continuous variables by means and standard deviations (SD), or the median and interquartile range (IQR) for those data not normally distributed (Kolmogorov-Smirnov test). Categorical variables were compared by chi-square test or Fisher's exact test where appropriate. Continuous variables were compared by Student´s t-test once normality was demonstrated; otherwise, the nonparametric Mann-Whitney U test was performed.

Univariate and multivariate logistic regression analyses were performed as an explanatory analysis to predict 30-day mortality (dependent variable) in patients with novel H1N1 associated pneumonia. The independent variables were: age, sex, pregnancy, duration of symptoms, previous antibiotic, structural lung disease, chronic heart failure, neurological disorder, alcoholism, radiography, temperature, leucocytosis, PO_2/FIO_2, mechanical ventilation and shock. Variables that showed a significant result univariately ($p<0.1$) were included in the multivariate logistic

regression backward stepwise model. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the model [8].

All tests were two-tailed and significance was set at 5%. All analyses were performed with SPSS version 16.0 for Windows. (SPSS Inc., Chicago, Illinois, USA).

Ethics

Antoni Torres has had access to and takes responsibility for the integrity of the data and the accuracy of the data analysis. This study was approved by Ethics Committee of Hospital Clinic and Hospital de Puerto Montt, Chile.

RESULTS

Comparison of patient characteristics

Of the 127 patients enrolled in the study, 52 were hospitalized for seasonal influenza (69.6 ± 17.0 years) and 75 for novel H1N1 influenza (39.7 ± 16.7 years; 75% (75/100) of all patients admitted with confirmed H1N1). All patients had radiologically confimed pneumonia. This was the cause for hospitalization in 96.2% versus 77.3% (p= 0.004) whereas the remainders were hospitalized essentially because of unstable comorbidity (3.8% versus 17.3%, p=0.021).

The main clinical characteristics are given in table 1. Chronic heart failure, structural lung disease, neurological disorders and alcoholism were more frequent in patients with seasonal influenza and asthma in those with novel H1N1. The latter presented more frequently with fever and tachycardia. Significant differences also related to the inflammatory response, with more novel H1N1 patients having leucocyte counts < 10,000/µL (61.6% versus 32.7%, p=0.001) and leucopenia< 4,000/µL (13.7% versus 0%, p=0.005). The most obvious differences were present in chest radiography. Alveolar infiltrates were more frequently present in patients with seasonal influenza (94.2% versus 46.7%, p<0.0001) whereas the pattern was more frequently interstitial and mixed in those with novel H1N1 (53.3% versus 5.8%, p<0.0001). Pleural effusion occurred in four patients with seasonal influenza as compared to none in novel H1N1 patients (p=0.026).

Comparison of pneumonia severity

Pneumonia severity at admission as reflected by CRB-65 and PSI score was higher in patients with seasonal influenza. Both older age and more comorbidities surely played an important role in determining higher severity scores in the group of seasonal influenza. Overall, 79 and 60% of patients with seasonal influenza had scores reflecting higher severity (CRB-65 > 1 and PSI IV/V), respectively, as compared to 51 and 19% in those with novel H1N1 influenza (table 2).

Low risk PSI classification was poorly sensitive in patients with novel H1N1: of those with novel H1N1 and low risk PSI classification (classes I-III), 21.3% (13/61) required ICU admission, 11.5% (7/61) mechanical ventilation, and 6.6% (4/61) died. The corresponding numbers for those with seasonal influenza were 0 for ICU admission and mechanical ventilation and 4.8% (1/21) for death.

In contrast, low risk CRB-65 classification (class 0) continued to be associated with low risk of complications or death also in novel H1N1 (no patient requiring ICU admission, mechanical ventilation and no death in those with novel H1N1 and three patients requiring ICU admission, none mechanical ventilation and no death in those with seasonal influenza) (table 2).

Microbiological findings

In 32/75 patients with novel H1N1 and 32/52 with seasonal influenza, blood cultures were retrieved. No pathogens were isolated.
Only two cases with seasonal influenza had a copathogen (Haemophilus influenzae and respiratory sincitial virus)

Antimicrobial treatment

All patients received antibacterial treatment according to the recommendations of national guidelines. In patients with novel H1N1 associated pneumonia, this included ceftriaxone monotherapy in 31 patients and ceftriaxone with quinolone combination therapy in 42 patients, one patient each received macrolide or quinolone monotherapy.
In patients with seasonal influenza, treatment was as follows: in Barcelona, 20 patients received quinolone or ß-lactam monotherapy, 22 patients combination therapy (11 ß-lactam/quinolone, 10 ß-lactam/macrolide, one quinolone/macrolide); in Puerto Montt nine patients received ceftriaxone monotherapy and one ceftriaxone combined with a macrolide.

None of the patients with seasonal influenza-associated pneumonia received antiviral treatment. In contrast, all patients with novel H1N1 associated pneumonia except one

(74/75) in Puerto Montt received antiviral treatment. Of these, 70 received oral oseltamivir, whereas 4 pregnant women received inhaled zanamivir. The one patient without treatment had a delayed diagnosis and was not treated in face of a favourable spontaneous clinical course.

Comparison of complications

Patients with novel H1N1 were admitted far more frequently at the ICU (29.3% versus 7.7%, p=0.003). Patients with novel H1N1 influenza had more frequently respiratory failure as reflected by PaO2/FIO2 < 200 (28.1% versus 11.6%, p=0.042) and required more frequently mechanical ventilation (18.7% versus 2%, p=0.005). Moreover, four patients with novel H1N1 received noninvasive ventilation as compared to only one in those with seasonal influenza (p=0.648). Septic shock was not different in both groups (n=5 (6.7%) versus n=2 (3.8%), p=0.699). Length of hospitalisation was not different between groups.

30-day mortality analysis

30-day mortality was higher in patients with novel H1N1 (12% versus 5.8%), however, this difference did not reach statistical significance (p=0.238). Death was attributable to influenza virus in 77.8% (7/9) in patients with novel H1N1 as compared to none in those with seasonal influenza (p=0.046).

Statistically significant variables in the univariate logistic regression analysis and multivariate logistic regression analysis of factors associated with death in patients with novel H1N1 associated pneumonia are given in table 3. An independent association with death was evident for previous antibiotic, PaO_2 / FiO_2 < 200, mechanical ventilation and septic shock. Mechanical ventilation was the only variable independently associated with death in multivariate analysis (table 3).

DISCUSSION

The main findings of this study are the following: 1) pneumonia associated with novel H1N1 influenza affected a population different from seasonal influenza, which basically was younger (mean 39.7 versus 69.6 years), with far less chronic comorbidity and alcoholism; 2) in clinical terms, these patients had less leucocytosis (32.7 versus 61.6%) as well as more extensive and frequently interstitial infiltrates; 3) pneumonia presented more frequently with respiratory failure, leading to a higher rate of ICU admission and ventilatory support, particularly mechanical ventilation (29.3 versus 7.7% and 18.7 versus 2%, respectively); also, need for mechanical ventilation was the only independent predictor of death in patients with novel H1N1 associated pneumonia; 4) accordingly, mortality was double as high in patients with novel H1N1 (12% versus 5.8%), and was attributable to pneumonia in most instances (77.8%); 5) CRB-65 but not PSI appropriately predicted low risk patients.

Seasonal influenza epidemics typically are characterized by a J-shaped hospitalization pattern, with high rates in ages below 5, low rates in ages 5 to 49, and a significant rise in those aged 50 or older. Since 1977, H3N2, H1N1, and B viruses have circulated, with epidemics of H3N2 infection causing the greatest morbidity in the elderly population. Elderly persons above 50 years may be relatively resistant to severe H1N1 disease because of an exposure prior to 1957 when these viruses circulated widely. Accordingly, the recent H1N1 global epidemic showed a change in age patterns with younger persons being frequently infected [3,4,9]. In fact, younger persons are particularly at risk of severe courses and death. In particular, pregnancy, although not significantly different in our series, was more frequent in patients with H1N1 (n=4 versus 0).

The classic description of influenza pneumonia was provided by Louria et al. after the 1957 H2N2 pandemic. Lower respiratory tract disease was classified into four categories: no radiographic pneumonia, viral infection followed by bacterial pneumonia, rapidly progressive viral pneumonia and concomitant viral-bacterial pneumonia. Mortality was reported to be relatively high [10]. These patterns, however, did not correspond to those typically observed in patients with seasonal influenza associated pneumonia, particularly in elderly patients [11, 12]. Prior to

significant antigenic shifts, previous exposure to influenza, including vaccinations, may have reduced the severity of influenza-associated lower respiratory tract disease [13].

The clinical presentation of patients with novel H1N1 associated pneumonia was different mainly in terms of a higher percentage of patients with pharyngitis as well as higher mean temperature and heart rate. Although age is a significant risk factor for the development of lower respiratory tract complications of influenza virus infection, pure viral pneumonia is relatively uncommon outside pandemic setting in immonocompetent hosts. Most elderly persons have partial immunity resulting from vaccination or natural infections [1]. Accordingly, radiographic infiltrates in seasonal influenza have been described as mostly limited, unilateral, and subtle [10]. The clinical presentation of our patients with H1N1, however, being characterized by less leucocytosis and more extensive, mostly interstitial radiographic affection, is well compatible with pure viral pneumonia of a nonimmune host.

We are unable to analyze the effect of antiviral treatment because virtually all patients with novel H1N1 associated pneumonia were treated with agents active against influenza virus. The higher mortality despite treatment compared to seasonal influenza may be due to novel H1N1 itself and does not allow any conclusion. However, some observational data support the use of antiinfluenza treatment also in patients with pneumonia [14].

The mortality rate in our population with novel H1N1 associated pneumonia (12%) is similar to that reported in previous series [3,4]. Attributable mortality reached 77.8%. Conversely, patients with seasonal influenza had low mortality (5.8%), and none of the three patients who died could be attributed to influenza virus infection itself. In multivariate analysis, acute respiratory failure as reflected by need for mechanical ventilation was the only independent predictor of death in patients with novel H1N1 associated pneumonia. This finding is well compatible with viral pneumonia (and not bacterial coinfection along with septic shock) being the principal cause of death in these patients.

Pneumonia severity assessment tools (PSI and CRB-65) predicted death roughly in a three class pattern as expected. However, death rates in higher risk classes were

higher than expected in patients with novel H1N1 associated pneumonia and reflected the higher absolute death rates in these patients. Of note, both scores performed equally well in patients with seasonal influenza classified as low risk, with only one death in the low risk PSI group. However, whereas CRB-65 continued perform well in patients with novel H1N1 pneumonia classified as low risk classes, high rates of complications and death occurred in the low risk PSI group. This finding may be explained by the fact that a zero CRB-65 score excludes the presence of the main vital sign abnormalities whereas these may be present in PSI risk classes II and III.

There are several limitations of our study. 1) the population with seasonal influenza was heterogeneous with regard to origin, year and seasonality which may have biased the comparator; however, our findings fit well with the clinical and outcome patterns of these patients expected; 2) diagnosis of seasonal influenza was based on paired serology using two different serologic methods and may therefore have missed cases with acute clinical course and early death; however, other series confirm the relatively low incidence and mortality of pneumonia associated with seasonal influenza [11]; 3) although the diagnostic approach applied included a search for copathogens in patients with seasonal influenza, patients with novel H1N1 were not subject to systematic investigation for copathogens, and we cannot exactly assess the proportion of patients affected by mixed viral/bacterial etiologies. Notwithstanding, all patients received antibacterial therapy in accordance with the current international recommendations. However, the clinical and radiological presentation in novel H1N1 influenza patients suggested pure viral pneumonia in most instances; 4) the international recommendations for H1N1 pandemic induced to systematically use antiviral treatment on hospitalized patients, differently by seasonal influenza. Unfortunately, the effect of differential use of antiviral is difficult to be estimated.

In conclusion, the main clinical patterns of pneumonia associated with novel H1N1 influenza differ characteristically from that known from seasonal influenza. Younger age, less comorbidity, more extensive radiographic extension and more severe respiratory compromise are key features. Pregnancy is an additional risk factor. Pneumonia severity is higher, particularly because of acute respiratory compromise, which is also reflected by a higher rate of ICU admission and need for ventilator support. Mortality is double that of seasonal influenza, both in terms of absolute rates

as well as pneumonia-related mortality. Our data indicate that PSI but not CRB-65 may underestimate the risk for complications and death in patients classified as low risk.

Author contributions

R. Riquelme and A. Torres had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

R. Riquelme: contributed to study concept and design; acquisition, analysis, and interpretation of data; drafting of the manuscript; and critical revision for important intellectual content.

C. Cilloniz, M. Riquelme, C. Inzunza, E. Polverino, Y. Gomez, C. Contreras: contributed to acquisition of data, drafting of the manuscript, and critical revision for important intellectual content.

A. Gabarrús: contributed to acquisition and analysis of data.

S. Ewig: contributed to study concept and design; interpretation of data; and critical revision for important intellectual content.

ML Rioseco, MA Marcos and R. Fascecontributed to microbiologic processing of samples; and critical revision for important intellectual content.

A. Torres: contributed to study concept and design, analysis and interpretation of data, statistical analysis, drafting of the manuscript, and critical revision for important intellectual content.

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Table 1. Characteristics of patients with novel H1N1 and seasonal influenza virus

Variable	Novel H1N1 influenza A (n=75)	Seasonal influenza A (n=52)	p-value
Age (years), mean (SD)	39.7 (16.7)	69.6 (17.0)	**<0.001**
Sex, male, n (%)	39 (52)	25 (48)	0.664
Length of stay (days), median (IQR)	6.0 (7.0)	6.5 (6.5)	0.217
Previous antibiotic, n (%)	9 (12)	7 (14)	0.797
Comorbidity, n (%)			
- structural lung disease	18 (24)	24 (46)	**0.009**
- chronic heart failure	0 (0)	9 (17)	**0.002**
- neurological disorder	3 (4)	11 (21)	**0.002**
- alcoholism	1 (1)	6 (12)	**0.016**
Pregnancy, n (%)	4 (5)	0 (0)	0.144
Influenza seasona lvaccination n(%)	11(16)	25(54)	**<0.001**
Pneumonia as cause of hospital admission, n (%)	58 (77)	50 (96)	**0.004**
Length of symptoms (days), median (IQR)	5.0 (5)	5.0 (3)	0.705
Clinical manifestations, n (%)			
- Pharyngitis	23 (31)	20 (39)	0.389
- Fever	72 (96)	39 (75)	**0.005**
- Cough	67 (91)	46 (89)	0.706
- Chills	32 (43)	20 (39)	0.653
- Dyspnea	48 (65)	37 (71)	0.458
- Chest pain	20 (27)	22 (42)	0.073
- Mental confusion	4 (5)	8 (15)	0.057
- Gastrointestinalsymptoms	18 (24)	8 (16)	0.264
Clinical findings			
- Temperature (°C), mean (SD)	38.1 (1)	37.7 (1.1)	**0.039**
- Respiratory rate (breaths per min), mean (SD)	29.2 (8)	28.2 (8.0)	0.486
- Systolic pressure (mmHg), mean (SD)	133.7 (24)	131.3 (22.5)	0.566
- Diastolic pressure (mmHg), mean (SD))	81.5 (19)	72.6 (11.5)	**0.001**
- Heart rate (breaths per min), mean (SD)	106.2 (22)	96.5 (17.6)	**0.009**
- Crackles, n (%)	53 (71)	18 (36)	**<0.001**
Laboratory findings			
- Leucocytes (µL), mean (SD)	9.689 (6.179)	13.512 (7.147)	**0.002**
- Serum-creatinine (µmol/L), median (IQR)	104.3 (39.8)	113.2 (26.5)	**<0.001**
- PaO_2 (mmHg), mean (SD)	77.0 (23.9)	59.5 (12.3)	**<0.001**
- $PaO_2FiO_2 < 200$, n (%)	18 (28)	5 (11)	**0.042**
Radiography, n (%)			
- Alveolar	35 (47)	49 (94)	**<0.001**
- Interstitial	21 (28)	3 (4)	**<0.001**
- Mixed	19 (25)	1 (2)	**<0.001**
Complications, n (%)			
- ICU admission	22 (29)	4 (8)	**0.003**
- Mechanical ventilation			
no	57 (76)	50 (96)	**0.003**
yes	14 (19)	1 (2)	**0.005**
yes, noninvasive ventilation	4 (5)	1 (2)	0.648
- Septic shock, n (%)	5 (7)	2 (4)	0.699

Note. ICU: intensive care unit. PaO_2 was on room air.

Table 2.

Comparison of pneumonia severity as assessed by PSI and CRB-65 score

	Novel influenza A (H1N1)				Seasonal influenza			
	N (% column)	ICU admission N (% row)	Mechanical ventilation N (% row)	Deaths N (row %)	N (% column)	ICU admission N (row %)	Mechanical ventilation N (row %)	Deaths N (row %)
CRB-65								
0	37 (49)	3 (8)	0(0)	0 (0)	10 (21)	0 (0)	0 (0)	0 (0)
1-2	36 (48)	17 (47)	13(36)	9 (25)	32 (67)	2 (6)	1 (3)	2 (6)
3-4	2 (3)	2 (100)	1(50)	0 (0)	6 (13)	2 (100)	0 (0)	1 (50)
Total	75 (100)	22 (29)	14(19)	9 (12)	48 (100)	4 (5)	1 (1)	3 (6)
PSI								
I-III	61 (81)	13 (21)	7(12)	4 (7)	21 (40)	0 (0)	0 (0)	1 (5)
IV	12 (16)	7 (58)	6 (50)	4 (33)	19 (39)	0 (0)	0 (0)	0 (0)
V	2 (3)	2 (100)	1 (50)	1 (50)	12 (21)	4 (33)	1(8)	2 (50)
Total	75 (100)	22 (29)	14 (19)	9 (12)	52 (100)	4 (8)	1 (2)	3 (6)

Note. CRB-65: Confusion, Respiratory rate, Blood pressure and Age >65years; PSI: Pneumonia Severity Index.

Table 3.

Significant univariate and multivariate logistic regression analysis of 30-day mortality for patients with novel H1N1

Variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Previous antibiotic	4.9	1.0 – 24.9	0.054			
PaO_2 / FiO_2 < 200	28.6	3.2 – 257.6	0.003			
Mechanical ventilation	40.0	4.5 – 352.9	0.001	28.0	3.1 – 251.9	0.003
Shock	16.0	2.2 – 115.3	0.006			

OR: Odds Ratio; CI: Confidence Interval