Rev Med Chile 2019; 147: 842-851

Host characteristics predict outcome among adult patients admitted by severe acute respiratory infection

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Financial source: none.

Recibido el 21 de marzo de 2019, aceptado el 19 de julio de 2019.

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ABSTRACT

***Background**: Except for influenza pandemics, different observational studies have failed to demonstrate differences in mortality between various etiologies in adult patients hospitalized for respiratory infections.* ***Aim**: To compare clinical and mortality differences between different viral pathogens associated with severe acute respiratory infections (SARI) in hospitalized adults.* ***Material and Methods:** One-year prospective study in a sentinel center. We included 132 patients with SARI hospitalized for any of the nine viruses under study by PCR. Clinical variables were compared, excluding cases of coinfection.* ***Results:** A viral coinfection was identified in 12% and influenza infection in 56% of cases. Eighty percent of patients were aged ≥ 65 years, with a high frequency of comorbidities, 27% were bedridden. Twenty four percent were admitted to critical care units, 20% required ventilatory assistance and 16% died. Cases occurred throughout the year, with an expected seasonal peak between autumn and spring and a predominance of infections not associated with influenza during summer months. In the multivariate analysis, only being bedridden was significantly associated with mortality at discharge (Odds ratio 23.46; 95% confidence intervals 3.33-165.12, $p < 0.01$), without association with age, comorbidity, viral pathogen involved, laboratory parameters, clinical presentation or CURB65 score. No major clinical dissimilarities were found between different viral pathogens.* ***Conclusions**: In our series of patients, mostly elderly, only bedridden status was significantly associated with mortality at discharge in patients hospitalized for SARI. Viral pathogens were not relevant.*

(Rev Med Chile 2019; 147: 842-851)

***Key words:** Bedridden Persons; Frail Elderly; Mortality; Respiratory Tract Infections; Virus Diseases.*

Características del huésped predicen el desenlace en adultos hospitalizados por infección respiratoria aguda grave

Los factores del huésped son más importantes que el tipo viral para predecir el desenlace en pacientes hospitalizados por infecciones respiratoria aguda grave. Exceptuando las pandemias de influenza, diferentes estudios observacionales no han logrado demostrar diferencias en mortalidad entre diferentes patógenos en pacientes adultos hospitalizados por infecciones respiratorias. ***Objetivo:** Com-*

parar diferencias clínicas y en mortalidad entre diferentes patógenos virales asociados a infección respiratoria aguda grave (IRAG) en adultos hospitalizados. ***Método:*** *Estudio prospectivo durante un año en un centro centinela. Se incluyeron casos de IRAG hospitalizados por alguno de los 9 virus bajo estudio por RCP. Se compararon variables clínicas y desenlace.* ***Resultados:*** *Ingresaron 132 pacientes con IRAG. Se identificó coinfección viral en 12,1% e infección por influenza en 56,1%. La mayor parte era de la tercera edad (80,3%) con una alta frecuencia de comorbilidad y 27,3% estaba postrado. Veintitres coma cinco por ciento ingresó a unidad de cuidados críticos, 19,7% requirió asistencia ventilatoria y 15,9% fallecieron. Los casos ocurrieron todo el año, con un aumento estacional esperado entre otoño y primavera y predominio de infecciones no asociadas a influenza en verano. En el análisis multivariado, sólo la postración se asoció significativamente a mortalidad al egreso (ORa 23,46 IC95 3,33-165,12, p = 0,002), sin asociación con la edad, comorbilidad, patógeno viral involucrado, parámetros de laboratorio, presentación clínica o puntuación CURB65. No se encontraron discordancias clínicas mayores entre diferentes agentes virales.* ***Conclusiones:*** *En nuestra serie de pacientes, mayoritariamente de la tercera edad, sólo la postración se asoció significativamente a mortalidad al egreso en pacientes hospitalizados por IRAG. El patógeno viral no resultó ser relevante.*

Palabras clave: *Infecciones del Sistema Respiratorio; Mortalidad; Virosis.*

Pneumonia, asthmatic crisis, influenza-like illness, chronic bronchitis exacerbation, and decompensated heart failure are possible manifestations of influenza and other respiratory virus infections among adult patients. All these microorganisms are able to provoke admissions to general wards or intensive care unit and sometimes death[1-8]. Observational studies focusing on specific microbial pathogens have demonstrated a high case-fatality rate among adult patients admitted with streptococcal bacteremic pneumonia (near 30%) or with cardiopulmonary syndrome by hantavirus infection (25-40%)[9-11]. Figures are lower when series of human rhinovirus or influenza infection are considered, even in pandemic situations (range 10-16%)[2,3,12] The higher risk associated to some specific pathogens is not so evident when prospective cohort studies are analyzed, probably by the dilution of different etiologies and small number associated to each group. Thus, several prospective studies have not demonstrated substantial mortality differences between bacterial and viral pathogens among patients hospitalized for community acquired pneumonia (CAP) or influenza-like illness (ILI)[7,8,13-15]. Despite the higher burden associated to seasonal influenza infection, comparison with other viruses such as human rhinovirus, has not found significant mortality differences among ICU-admitted patients[13]. Yet, recent studies have shown the relevance of viral pathogens among adult patients admitted for CAP with incidence rates surpassing those associated to bacterial microorganisms[5]. Respiratory syncytial virus and parainfluenza virus appear to be equally contributory than influenza infection to explain seasonal mortality in elderly persons in population studies, and other studies have indicated that viral-bacterial co-infection is more important than the specific virus involved to predict mortality among those admitted by pneumonia[16,17]. Thus, excepting pandemic conditions, it is not clear if seasonal influenza is associated with a higher death toll than other viral microorganisms or if different types and subtypes of influenza virus differs each other in mortality among admitted adult patients. This is a relevant question because comparable outcomes would mean to intensify efforts for vaccine and drug development also targeting non-influenza respiratory viruses and to enhance prevention during social interactions. Using data obtained form an active surveillance network to monitor admitted patients with severe acute respiratory infections (SARI) in one sentinel hospital in Chile[18], we analyzed clinical features and prospectively compared mortality associated to influenza and other respiratory viruses for one year.

Patient and Methods

This descriptive observational study used data from the SARI surveillance network complemented by information obtained from reviews of individual medical records. Researchers identified adult patients hospitalized with SARI between January to December 2015 at Hospital Militar, a SARI sentinel surveillance hospital in the Metropolitan area of Santiago, Chile.

Inclusion/exclusion criteria, case definition, and laboratory testing

SARI cases were identified using the following standard case definition: measured/reported history of fever plus respiratory symptoms associated with tachypnea (≥ 30 breaths/minute) and/or low pulse oximetry (blood oxygen saturation < 90% while breathing ambient air)[18]. However, fever was a conditional inclusion criterion, left to the discretion of the physician in charge of case recruitment.

Nasopharyngeal swab specimens collected from patients that met the SARI criteria were analyzed first by direct immunofluorescence (IF; Diagnostic Hybrids, Quidel) for eight different viruses: influenza A and B, human parainfluenza virus (HPIV) 1-3, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and human adenovirus (HAdV). All samples positive for influenza or for other virus, as well as those negative for all respiratory viruses were processed further at the national reference laboratory (*Instituto de Salud Pública de Chile*), using real time polymerase chain reaction (RT-PCR) to detect influenza A or B, HPIV 1 to 3, RSV, HAdV, hMPV and human rhinovirus (HRV), and perform viral subtyping for influenza A virus. Kits for RT-PCR were provided by the CDC, Atlanta, USA (Kit KK0813 for non influenza respiratory virus and Kits FR-198 for influenza virus and FR-1526 for influenza A subtyping, respectively). All adult patients with SARI and a positive result by RT-PCR for any of the 9 viruses under study were included. Cases with incomplete information or readmissions were excluded.

Clinical characterization, management, and outcome

This part of the study has been previously detailed[3]. Clinical presentation was classified in mutually exclusive groups: influenza-like illness (ILI), asthmatic crisis; chronic bronchitis exacerbation; pneumonia (chest x-ray available for all patients), and cardiovascular decompensation[3]. Data on variables associated with disease management (need for invasive or noninvasive mechanical ventilation; vasoactive drugs and antiviral (oseltamivir) compounds prescription were also obtained. Site of hospitalization (critical care units or general ward) was also recorded, along with the CURB-65 pneumonia severity score[19], and outcome at discharge (deceased or alive).

Statistical analysis

Different complementary analyses were made for more robust conclusions. First, we analyzed potential factors associated to a fatal outcome for the whole group, including comorbid conditions, immunization record, clinical features, laboratory parameters, admission to CCU beds, ventilatory assistance, antiviral use and information on viral pathogens. This approach was needed to identify relevant risk factors for a fatal outcome. Those factors identified by univariate analysis ($P < 0.10$) were integrated in a multivariate analysis by binary logistic regression. For this part of the work, cases with viral coinfection were not excluded.

Second, to explore relevant disparities between different viral pathogens associated to SARI, previously detailed variables were compared between patients with influenza infection (any type/subtype) versus those affected with other viruses, between those affected by influenza A vs influenza B infection, and between patients with influenza AH1Npdm09 versus non-influenza virus infection. This part of the analysis was performed excluding cases with known viral coinfection.

Comparisons were made trough contingency tables using chi square test and odds ratio (OR) calculated. When any cell of the contingency tables displayed 0 counts, 0.5 cases for every cell were added to avoid OR with infinite limits for the IC95.

Curves of incidence for different group of respiratory viruses were obtained trough distance-weighted least square fitting to facilitate interpretation

Ethics approval

This study was approved by the Hospital Militar Institutional Review Board and, as a retrospective analysis of the data, deemed exempt from the

informed consent requirement. Patient anonymity was assured during the analysis.

Results

Global results

During year 2015, nasopharyngeal PCR identified 132 adult admitted patients with SARI associated to one or more of the 9 viruses under study. Influenza A/B explained half of the detected virus (Table 1). HAdV, HRV, RSV, HPIV 1 to 3, and hMPV were also identified. Viral co-infection was detected in 16 patients (12.1%) IF testing detected only 20 patients with influenza infection (27% sensitivity) and 11 with non-influenza viruses (35.5% sensitivity for RSV, 66.7% for hMPV, 4% for HAdV, 100% for HPIV2, and 9.1% for HPIV3). The population under study was elderly (mean age 77.1 years old, 80.3% ≥ 65 years old) and with a high frequency of chronic conditions (heart disease 41.7%; lung diseases 32.6%; neurological 26.5% or diabetes mellitus 23.5%). Besides, 27.3% were bedridden. CAP was the most common form of presentation (n = 66; 50%) followed by ILI and exacerbated chronic bronchitis (n = 21; 15.9% each group, respectively). Some patients presented with decompensated heart failure (n = 7; 5.3%), asthmatic crisis (n = 6; 4.5%) or other conditions (11; 8.3%). Of the whole group, 31 patients (23.5%) were admitted to intermediate or critical care beds, 26 needed ventilatory assistance (invasive or non-invasive; 19.7%), and 21 died (in-hospital mortality 15.9%). Seasonal analysis showed a high expected incidence during autumn and winter months for influenza and non-respiratory influenza viruses (Figure 1). However, the latter group had a bimodal distribution with a second peak on summer months. Viral coinfection was concentrated in autumn and winter. Blood cultures were taken in 114 patients (86.4%) and in only 4 cases were positive (3%), only one of them among patients with influenza infection. Bacterial species involved were *Streptococcus pneumoniae* (2 cases), *S. aureus* and *K. pneumoniae* (one each).

Table 1. Virus distribution among 132 adult patients admitted by SARI at Hospital Militar, Santiago, Chile 2015

Virus / virus subtype	n	%
Influenza virus		
Influenza A H1N1pdm09	16	12.1%
Influenza A H1N1pdm09 with viral coinfection*	9	6.8%
Influenza A H3N2	32	24.2%
Subtotal Influenza A	57	43.2%
Influenza B	17	12.9%
All influenza viruses	74	56.1%
Other respiratory viruses		
Human adenovirus	18	13.6%
Human rhinovirus	11	8.3%
Respiratory syncytial virus	10	7.6%
Human parainfluenza virus 3	7	7.3%
Human metapneumovirus	2	1.5%
Human parainfluenza virus 1	2	1.5%
Human parainfluenza virus 2	1	0.8%
Non-influenza viral coinfection**	7**	5.3%

*with RSV in 4 cases, HRV in 1 case, with HPIV3 in 1 case, with HAdV and RSV in 2 cases, and with HRV and RSV in 1 case; **HAdV and HPIV3 in 3 cases, HAdV and RSV in 2 cases, HPIV1 and hMPV in 1 case and HPIV1 and RSV in 1 case.

Analysis of factors associated to a fatal outcome in the whole group

This part of the work excluded one patient due to her transfer to another hospital leaving 131 for analysis. Demographic and comorbid conditions, clinical features, laboratory parameters, positive blood cultures, viral coinfection, seasonal influenza vaccine records, admission to CCU and early oseltamivir use (until 3 days of symptoms started), were analyzed in order to identify factors associated to death. The following factors turned to be significant after univariate analysis: bedridden status, increased plasmatic creatinine concentration, low platelet count, hypoalbuminemia, pulse oximetry < 90%, CURB 65 score ≥ 3 points, and presence of pneumonia (Table 2).

A multivariate analysis was then performed using binary logistic regression, incorporating the significant factors identified from the univariate analysis and relevant variables for appropriate adjusting (gender, older age, presence of any risk factor, infection by influenza virus and influenza seasonal vaccine). Of them, only being bedridden (OR 23.46; IC95 3.33-165.12) was independently associated with a fatal outcome (Table 2). The inclusion of other adjusting variables such as infection by influenza A H1N1pdm09 and viral coinfection did not modify the observed results (data not shown).

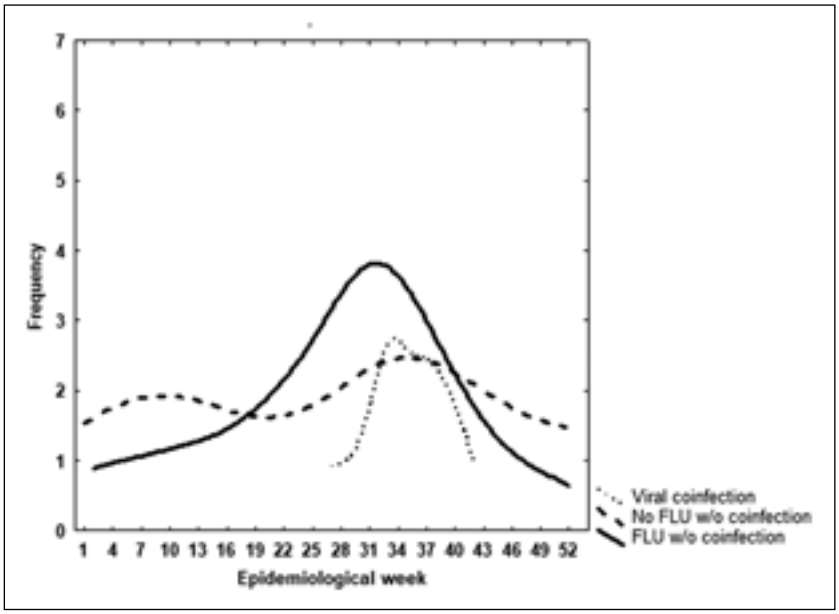

Figure 1. Seasonal distribution of cases admitted by SARI according to different respiratory viruses, Hospital Militar, Chile, 2015. No FLU w/o coinfection: non-influenza respiratory viruses without viral coinfection; FLU w/o coinfection: influenza virus without viral coinfection. Curves were obtained trough distance-weighted least square fitting to facilitate interpretation.

Table 2. Factors associated to a fatal outcome among patients admitted by SARI, Hospital Militar, Chile 2015

Factor	Deceased n/N*	Non-Deceased n/N*	OR	IC95	p value**
Univariate Analysis					
Female gender	11/21	60/110	0.91	0.36-2.33	ns***
Age ≥ 65 years old	18/21	90/110	1.33	0.35-4.96	ns
Any risk condition****	20/21	104/110	1.15	0.13-10.11	ns
Infection by influenza virus with/without coinfection	13/21	61/110	1.30	0.50-3.40	ns
Any viral coinfection	3/15	18/116	1.36	0.35-5.31	ns
Influenza seasonal vaccine	3/16	35/101	0.43	0.11-11.63	ns
Bedridden	15/21	21/110	10.59	3.67-30.56	< 0.001
Increased creatinine concentration (> 1 mg/dL)	15/21	43/107	3.72	1.33-10.34	0.009
Low platelet count < 150 000/μL	7/19	14/109	3.95	1.33-11.75	0.009
Hypoalbuminemia (< 3.5 g/L)	12/20	23/103	5.21	1.90-14.29	0.001
Pulse oxymetry < 90%	19/20	78/110	7.79	1.00-60.74	0.023
CURB 65 score ≥ 3 points	16/21	36/109	6.48	2.20-19.11	< 0.001
Pneumonia	16/21	50/110	3.84	1.31-11.21	0.010
Multivariate analysis			aOR		
Bedridden			23.46	3.33-165.12	0.002*****

*Numbers of patients with available information; **p values were obtained by Chi square on contingency tables; ***ns non-significant; ****older age, chronic disease conditions, cancer, obesity, pregnancy or immune suppression. Significant variables associated to a fatal outcome after multivariate analysis is indicated in bold type; *****p value obtained by binary logistic regression. Table was prepared by authors.

Influenza A/B infection compared with other respiratory viruses

During the study period, 116 patients were admitted by SARI associated to different respiratory viruses without viral coinfection. Basal patient´s characteristics and comorbid conditions were similar between those affected by influenza virus when compared with those infected by other respiratory viruses (Table 3). Clinical features were similar except for the significant lower rate of rhinorrhea (OR 0.30; IC95 0.12-0.73, p = 0.007) and ILI among patients with influenza (OR 0.27; IC95 0.09-0.76, p = 0.01). Frequencies of CAP, decompensated heart failure, exacerbated chronic bronchitis or asthmatic crisis were not different (data not shown). In the same manner, rates of hypotension, leukocytosis, lymphopenia, thrombocytopenia, hypoalbuminemia, and increased plasmatic values for LDH and creatinine were similar between groups. Use of intensive resource and outcome were comparable (Table 4).

Table 3. Comparison of demographic and comorbid conditions between 116 patients admitted by SARI associated to different viral pathogens, Hospital Militar, Chile 2015. Cases with coinfection were excluded

Factor	Influenza A or B n/N	Other respiratory virus n/N	OR	IC95	p value*
Age; average (range) in years	75.8 (26-99)	79.2 (54-97)	-	-	ns
Age ≥ 65 years	51/65	45/51	0.48	0.17-1.37	ns
Female	37/65	27/51	1.17	0.56-2.45	ns
Smoking (previous or current)	8/65	8/51	0.75	0.26-2.17	ns
Ethanol consumption	0/65	2/51	0.15**	0.001-3.20	ns
Chronic obstructive pulmonary disease	21/65	17/51	0.95	0.43-2.08	ns
Asthma	8/65	2/51	3.43	0.69-19.96	ns
Any respiratory condition	29/65	19/51	1.35	0.64-2.87	ns
Heart disease	22/65	23/51	0.62	0.29-1.32	ns
Chronic neurological disease	12/65	16/51	0.49	0.20-1.17	ns
Diabetes Mellitus	14/65	15/51	0.65	0.28-1.53	ns
Chronic kidney disease or dialysis	5/65	6/51	0.62	0.18-2.17	ns
Cancer	3/65	4/51	0.57	0.12-2.66	ns
Immune suppression by disease or drugs	5/65	5/51	0.77	0.21-2.80	ns
Obesity	1/65	2/51	0.38	0.03-4.34	ns
Liver disease	0/65	2/51	0.15**	0.001-3.20	ns
Bedridden	13/65	18/51	0.45	0.19-1.05	ns
Long-term care residence	4/65	3/51	1.05	0.22-4.91	ns
Domiciliary oxygen use	4/65	5/51	0.60	0.15-2.37	ns
Any risk condition***	58/65	51/51	0.08	0.00-1.44	ns
One risk factor	10/65	6/51	1.36	0.46-4.04	ns
Two risk factors	24/65	20/51	0.90	0.42-1.93	ns
≥ 3 risk factors	24/65	25/51	0.60	0.28-1.28	ns
Length of stay in days mean (range)	10.6 (1-61)	10.6 (1-44)	-	-	ns

*p values were obtained by Chi square on contingency tables; **OR were calculated assigning 0.5 to every cell to allow a finite number; ***older age, chronic disease conditions, cancer, obesity, pregnancy or immune suppression.

Table 4. Comparison of severity scores, use of hospital resources and outcomes between 116 adult patients admitted for SARI associated to different viral pathogens to the Hospital Militar, Santiago, Chile 2015. Cases with coinfection were excluded

Variable	Influenza A or B n/N	Other respiratory virus n/N	OR	IC95	p value*
CURB 65 severity score					
Score 0-2	41/64	28/51	1.46	0.69-3.10	ns
Score ≥ 3	23/64	23/51	0.68	0.32-1.44	ns
Admission to CCU beds	15/65	10/51	1.23	0.50-3.02	ns
Ventilatory assistance	12/65	8/51	1.21	0.45-3.24	ns
Deceased	12/65	6/51	1.69	0.59-4.88	ns

*p values were obtained by Chi square on contingency tables.

Comparison of patients infected by different influenza type viruses

After excluding cases with viral co-infection, 48 patients were registered with SARI secondary to influenza A and other 17 with influenza B infection. Comparison of them for demographic features and basal comorbid conditions did not show significant differences (data not shown), except for a lower rate of chronic lung conditions in the subgroup with influenza A infection (12 out of 48 versus 9 of 17; OR 0.29 IC 0.09-0.94; p = 0.037). Also, laboratory parameters were similar between both groups (data not shown). Clinical presentation was also similar as well as CCU bed requirement, ventilatory assistance and in-hospital mortality (data not shown). Ten out of 48 patients with influenza A died compared with 2 of 17 with influenza B infection (OR 1.97; 0.38-10.08) Rates of seasonal influenza vaccine for those with available information (15 out of 44 and 5 out of 17, respectively) and early oseltamivir therapy were also similar (data not shown). In total, only 20 of 61 patients with influenza received seasonal vaccine.

Comparison of patients with influenza A H1N1pdm09 and other respiratory viruses

Sixteen patients admitted with influenza A H1N1pdm09 and without viral coinfection were identified during year 2015. This group was compared with those patients affected by non-influenza respiratory viruses. As in previous comparison there was no remarkable difference in comorbid conditions, clinical presentation, laboratory parameters, admission to CCU beds or outcome (data not shown). The only striking differences were associated to the lower age (mean age 66.5 vs 79.2 years old, p = 0.002), fewer prevalence of risk factors (OR 0.11 IC95 0.00-0.18, p = 0.012), and a lower rate of rhinorrhea (OR 0.11 IC95 0.01-0.91, p = 0.02) and bronchial obstructive signs (OR 0.30 IC95 0.09-0.99, p = 0.04) in those infected by influenza A H1N1pdm09.

Discussion

In hospital-mortality in this cohort of adult patients admitted was significantly associated to a bedridden status. This condition could be a proxy of different neurological, nutritional and/or immunological disarrangements. It has been demonstrated that these patients have higher prevalence rates of hypoalbuminemia and undernutrition and markedly altered or abolished swallowing and cough reflexes[20,21]. The absence of cough, the possibility of a diminished febrile response by sarcopenia and communication problems with caregivers could delay medical consultation and worsen prognosis. At least three research groups have previously reported that a bedridden status is an independent risk factor for mortality among admitted adult patients with CAP, although with a low or nil inclusion of patients affected by viral pathogens[22-24]. Bedridden patients will increase in the near future due to demographic changes

at a global scale and the impact on mortality by respiratory infections could get worse.

Results of this work suggest that specific respiratory viruses are not relevant to predict outcome among adult patients admitted by SARI. Instead, host factors appeared to be more relevant to forecast survival in our predominately elderly population. Remarkably, in our setting different respiratory viruses were associated to admission in critical care units and to a case-fatality rate surpassing 10% of the cohort. These numbers replicate previous reports[8,16,17] and underline the significance of non-influenza respiratory besides influenza as agents capable of originate mortality, hospital admissions, and consumption of critical hospital resources among adult patients[3,5,7,8].

Despite seasonal variation and higher incidence during cold months, our vulnerable patients were infected during the whole year. SARI admissions were also observed during the summer season albeit less associated to influenza virus or viral coinfection. Presence of a wide array of viral pathogens in patients admitted by SARI indicates on one side, the need of a rapid access to diagnostic tools with high sensitivity and specificity for several agents, and on the other side early empirical antiviral therapy. Despite a favorable impact on mortality, only drugs against influenza are available at this moment[25-27]. Several compounds against other respiratory viruses, especially for HRV or RSV are currently being investigated in a preliminary basis or have faceted safety issues[28-32]. Ribavirin, a wide spectrum antiviral compound explored in infants and immunocompromised patient with RSV infection, is cumbersome to use, costly and with a not well-established clinical efficacy, except perhaps those with hematopoietic stem cell transplantation[33,34]. Thus, the current inability to treat patients without influenza and the need of early antiviral treatment for influenza leaves prognosis mainly depending on supportive care.

Seasonal influenza vaccine has a profound impact on reducing hospitalizations and mortality among vulnerable groups[3,35-38]. However, effectiveness of the seasonal influenza vaccine is reduced by the participation of other pathogens in respiratory infections (near 50% in our series), by the low coverage of the population with vaccine indication (near 30% in this work), non concordance between antigenic vaccine composition and circulating virus types, and by the suboptimal efficacy even when adequate matching is observed. Candidate vaccines for other respiratory viruses are still under development[29,39].

Only minor differences were identified in this work between alternative agents. Of interest, rhinorrhea and ILI were significantly less associated to influenza than other viruses (OR 0.30 and 0.10, respectively) suggesting in the case of influenza, predominance of lower respiratory infections, a masked clinical course and the need of a high level of suspicion. Infection associated to influenza A H1N1pdm09 affected younger patients and those without risk factor for a complicated evolution as described by others[15]. Older individuals had lower rates of infection and less severe disease during the first wave of the 2009 influenza pandemics due to a cross protective immunity generated by previous AH1N1 seasonal influenza infections[40]. This mechanism probably explains the underrepresentation of older individuals with SARI associated to influenza AH1N1pdm09.

This study had several limitations. Most patients were elderly, so there were not enough younger people in this patient group to investigate if older age was linked to a higher mortality rate. Second, the search for viral or bacterial coinfection was mainly restricted to blood cultures, which led to another study limitation. However, blood cultures were collected from near 90% of patients and only a small fraction (3%) were positive for bacterial species.

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