BRIEF COMMUNICATION

Ventilator-Associated Pneumonia in Patients with 2009 Pandemic Influenza A (H1N1) Infection: An Observational Study

D. CURCIO [1] - L. FERREIRA CABRERA [2] - A. DUARTE [3] - E. VALENCIA [4] - C.H. PAZ CHÁVEZ [5] - C. IBÁÑEZ-GUZMÁN [6] - M. JÁTIVA [7] - L. SOTO GERMANI [8] - J.C. FERNÁNDEZ MERCADO [9] - Z.U. CONTRERAS [10] - F. MOLINA SALDARRIAGA [11] - I. RAMOS PALOMINO [12] - A. ALÍ [13]

The 2009 pandemic influenza A (H1N1) virus has emerged to cause the first pandemic of the 21st century. As of mid-November, approximately 500,000 confirmed cases of 2009 pandemic influenza A (H1N1) infection had been reported to the World Health Organization (WHO). The true worldwide disease burden is yet unknown, but at least 100 times more people than those reported to the WHO have already been infected with this virus [1].

Most clinical disease is relatively mild but complications leading to hospitalization, with the need for intensive care, can occur, especially in very young children, during pregnancy, in morbid obesity, and in those with underlying medical conditions such as chronic lung and cardiac diseases, diabetes, and immunosuppression. Pneumonia is the most common and serious complication of the 2009 influenza A (H1N1) and it has played a significant role in fatal cases [2]. The clinical course of some cases was characterized by severe pneumonia, hypoxemia with multifocal infiltrates on chest x-ray, and rapid progression to acute respiratory distress syndrome and renal or multi-organ failure with requirement of advanced mechanical ventilation [3].

The aim of this study was to describe the epidemiological characteristics, clinical features, antibiotic treatment and outcomes of patients with confirmed 2009 influenza A (H1N1) infection complicated by ventilator-associated pneumonia (VAP).

The participating hospitals were from Argentina (n=2), Bolivia (n=1), Chile (n=2), Colombia (n=5), Ecuador (n=1), and Perú (n=2). The physicians used a standardized website form (http://www.clinicalrec.com.ar) that included demographic data, influenza-vaccination history for the previous year, risk factors for influenza disease, severity of illness at admission (measured by the APACHE II and SOFA scores), length of stay, microbiological documentation of VAP, antibiotic treatment and clinical outcomes.

Established criteria were used to define VAP [4]. Bacterial identification and susceptibility testing was performed according to the clinical microbiology procedures handbook [5].

Outcomes were defined as clinical success (partial or complete improvement of signs/symptoms of infection), clinical failure (no improvement or deterioration of signs/symptoms of infection), or indeterminate.

The study was based on a anonymous case registry methodology and did not require the prescription of specific drugs or other treatments, nor the performance of procedures or diagnostic tests other than the ones prescribed by the responsible physician; therefore inform consent was not required by the institutional review board from the participating institutions.

Results are expressed as proportions. When applicable, two tailed hypothesis testing for difference in proportions was used (Proportion Test); a p value of <0.05 was considered significant.

Thirteen intensive care units (ICU) participated and recruited 59 adults patients (18y) with real-time RT-PCR-confirmed infection with 2009 influenza A (H1N1) and requirement of respiratory support in the form of invasive ventilation admitted during the period June 10th and Septembre 15th 2009. All patients requiring had chest radiograph findings consistent with a diagnosis of acute respiratory distress syndrome.

Patients' median age was 45.6 years (range 18-80; SD ± 14.9); 29 were males (49%).

The median APACHE II score at admission was 18.2 (range 1-39; SD ± 9.9) (<15 in 26/59 patients –44%-, and 15 in 33/59 patients -66%-) (*Table 1*). In relation with the SOFA score at admission the median was 8.5 (range 2-18; SD ± 3.6) (*Table 1*).

In this patient population, the prevalence of risk factors for influenza disease 68% (40/59) (*Table 1*). Obesity (defined as a body mass index of >30m/kg), asthma, and diabetes mellitus, chronic obstructive were the risk factors more frequently observed (50% -20/40-, 42.5% -17/40- and 25% -10/40- respectively). No patient had received influenza-vaccination during the previous year, also, no patients had pathogens isolated in the respiratory samples taken at admission.

The mean of days of mechanical ventilation (MV) and length of stay (LOS) was 10.9 days (range 1-72; SD ± 11.63) and 12.3 days (range 1-72; SD ± 12.5) respectively.

Fifty-four percent of the patients (32/59) had VAP as nosocomial complication. The mean ICU stay before diagnosis of VAP was 9.5 days (range, 5-16).

In 31/32 patients (97%) 41 microorganisms considered as the causative agent of the infection were isolated (monomicrobial 69% [22/32] and polymicrobial 31% [10/32]). Among these isolates, *Acinetobacter* spp. (72%, 23/32; in 37% of cases carbapenem-resistant), methicillin-resistant *Staphylococcus aureus* (37.5%, 12/32), and extended-spectrum β-lactamase-producing Enterobacteriaceae (10%, 13/132) were the most common microorganisms, followed by *Pseudomonas aeruginosa* (6%, 2/32, in both cases carbapenem-susceptible) and *Stenotrophomonas maltophilia* (3%, 1/32).

Seventeen patients (53%) had VAP with bacteremia; in all cases with positive blood cultures for *Acinetobacter* spp.

Overall, attending physicians reported clinical success in 28 patients (47.5%). The clinical success rate showed no significant difference between patients with or without VAP (47% vs 48%, p= 0.6049; 95% CI= -0.27-0.24), as well as in patients with bacteriemic and non-bacteriemic VAP (35% vs 60%, p= 0.2971; 95% CI= -0.59-0.09) (*Table 1*).

The global mortality was 49% (29/59 patients) without significant differences between patients with or without VAP (59%

[1] Instituto Sacre Cour, Argentina; [2] Hospital Guillermo Grant Benavente, Chile; [3] Hospital Regional Río Grande, Argentina; [4] Clinica Sagrado Corazón, Colombia; [5] Hospital Central de la Fuerza Aérea y Clinica San Gabriel, Perú; [6] Hospital Obrero Nº 1, Bolivia; [7] Hospital Eugenio Espejo, Ecuador; [8] Hospital San Pablo De Coquimbo, Chile; [9] Clínica Crecer, Colombia; [10] Clinica Universitaria del Norte de Santander, Colombia; [11] Clínica Universitaria Bolivariana, Colombia; [12] Clínica San Gabriel, Perú; [13] Fundación Cardioinfantil, Colombia.

Correspondence: Daniel Curcio, Santo Tomé 5239 4to 22 (1419), Capital Federal. Argentina. Phone: 5411-4567-4426. FAX: 5411-4001-0781. e-mail: djcurcio@gmail.com

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vs 37%, p= 0.1475; 95% CI=-0.03-0.48), as well as in patients with bacteriemic and non-bacteriemic VAP (76.5% vs 40%, p= 0.0826; 95% CI=-0.08-0.02) (*Table 1*).

All patients received at admission a first antibiotic treatment for community-acquired pneumonia (CAP). Based on this data, we divided the patients into three groups according to the number of antibiotic courses received: Group I (27/59; 46%): patients whitout VAP who received only one course of antibiotics directed to CAP (average of 10.4 days); Group II (25/59; 42%): patients with VAP who received 2 courses of antibiotics for an average of 18.7 days (the first directed to CAP and the second to VAP due to nosocomial pathogens), and Group III (7/59; 12%): patients with VAP who received 3 courses of antibiotics for an average of 26.4 days (the first directed to CAP, the second to VAP due to nosocomial pathogens and the third as a last resort treatment for VAP) (p 0.0000) (*Table 2*).

Neuraminidase inhibitors (ozeltamivir 75mg q12 in 53/59-90%- and 150 mg q12 in 6/59-10%-) were initiated in all patients at admission and concomitantly with the first course antibiotic treatment.

TABLE 1- *Characteristics of 59 hospitalized patients who were infected with influenza A (H1N1)*

	Global and Sub-set of patients						
	Global (n=59)	**VAP (n=32)**	**Non-VAP (n=27)**	***p***	**Non-bacteriemic VAP (n=15)**	**Bacteriemic VAP (n=17)**	***p***
Male; *n (%)*	29 (49)	17 (53)	12 (45)	0.6869	8 (54)	9 (53)	0.7393
Age; *mean (range)*	45.6 (18-80)	47.5 (18-80)	43.7 (18-73)	0.2711	46 (18-80)	49 (18-73)	0.2436
Risk factors; *n (%)*	40 (68)	20 (61)	20 (74)		8 (53)	12 (70.5)	
APACHE II; *mean (range)*	18.2 (1-39)	18.4 (1-39)	18 (3-36)	0.7990	17.8 (1-36)	19 (1-39)	0.6098
• *≤15*	26 (44)	13 (41)	13 (48)	0.7515	7 (47)	6/17 (35)	0.7695
• *>15*	33 (56)	19 (59)	14 (52)	0.7515	8 (53)	11/17 (65)	0.7695
SOFA; *mean (range)*	8.5 (2-18)	8 (3-16)	9 (2-18)	0.2244	8.8 (2-18)	7.2 (3-16)	0.2539
Days of MV, *mean (range)*	10.9 (1-72)	11.9 (1-46)	9.77 (1-72)	0.6588	13.3 (1-46)	9.8 (1-34)	0.9803
LOS; *mean (range)*	12.3 (1-72)	13.2 (1-46)	11.4 (1-72)	0.7732	15.1 (1-72)	11.3 (1-34)	0.4698
Outcomes							
• *Clinical success*	28 (47.5)	15 (47)	13 (48)	0.8697	9 (60)	6/17 (35)	0.2971
• *Failure*	30 (51)	17 (53)	13 (48)	0.9048	6 (40)	11/17 (65)	0.2971
• *Indeterminate*	1 (2)	0	1 (4)	0.9316	0	0	NA
Mortality; *n (%)*	29 (49)	19 (59)	10 (37)	0.1475	13 (76.5)	6 (40)	0.0826

VAP=ventilador-associated pneumonia; LOS=length of stay

TABLE 2 - *Antibiotic treatment of 59 hospitalized patients who were infected with influenza A (H1N1)*

	Group I (n=27)	**Gruop II (n=25)**	**Group III (n=7)**
First course of antibiotic			
• Ceftriaxone + macrolides or fluorquinolones; *n (%)*	18 (66)	18 (72)	7 (100)
• Piperacillin/tazobactam + macrolides; *n (%)*	5 (19)	4 (16)	0
• Fluorquinolones alone; *n (%)*	4 (15)	3 (12)	0
Days; mean (*range*)	10.4 (1-20)[1]	7.88 (1-14)[2]	5.6 (1-13)[3]
Second course of antibiotic			
• Vancomycin + carbapenems; *n (%)*	NA	12 (48)	3 (43)
• Vancomycin + pip/taz or BEC; *n (%)*	NA	10 (40)	3 (43)
• Carbapenems alone; *n (%)*	NA	3 (12)	1 (14)
Days; mean (range)	NA	10.8 (2-25)[2]	11.5 (1-17)[3]
Third course of antibiotic			
• Tigecycline alone; *n (%)*	NA	NA	2 (28.5)
• Tigecycline + colistin; *n (%)*	NA	NA	3 (43)
• Tigecycline + aminoglycosides; *n (%)*	NA	NA	2 (28.5)
Days; mean (range)	NA	NA	9.3 (5-20)[3]

Group I: patients without VAP who received only one course of antibiotics; Group II: patients with VAP who received 2 courses of antibiotics; and Group III : patients with VAP who received 3 courses of antibiotics.

BEC=broad-spectrum cephalosporins

1 vs 2y3 p 0.0000

Like seasonal flu, the 2009 influenza A (H1N1) was mild and self-limiting in a great majority of cases, with only 1%-2% of our patients requiring hospitalization. Approximately 9 to 31% of hospitalized patients have been admitted to an ICU [6,7], where 56 to 81% of patients required respiratory support in the form of invasive ventilation [6,8,9]. In our series we found that a clinical diagnosis of VAP was established in 44% of patients. Similar, Koegelenberg *et al.* have published that one of the most frequent complications in patients with confirmed 2009 influenza A (H1N1) infection were the VAP (10/19, 52.6%) [10].

In accordance with other authors few patients older than 60 years in this study were admitted to the ICU (8/59; 13.5%) (data not shown). A potential biological basis for this observation is that patients in this age group have a cross-reactive antibody to 2009 influenza A (H1N1) at much higher rates than younger patients [11].

Acinetobacter spp. (in 37% of cases carbapenems-resistant) and MRSA were the most common microorganisms isolated in our patients with VAP. This is not surprising since, beyond the Latin American epidemiology, MDR *Acinetobacter* spp. and *P. aeruginosa*, MRSA and extended-spectrum β-lactamases-producing Enterobacteriaceae are the most common microorganisms isolated in this type of patient [12].

Logically patients with VAP received an additional course of broad-spectrum antibiotics following the antimicrobial therapy indicated at admission. Vancomycin (in combination carbapenems [imipenem or meropenem]; piperacillin- tazobactam or broad-spectrum cephalosporins) and carbapenems alone were the antibiotics most frequently prescribed (88% and 12% of patients who received 2 course of antibiotics, and 86% and 14% of patients who received 3 courses).

It is well-established that the early effective therapy for infections in critically ill patients with VAP (defined as antimicrobial treatment that covers the infecting pathogens) is associated with low mortality rates [13], however, the problem of bacterial resistance in Latin America means that physicians should improve the way they use antibiotics frequently associated with ecological collateral damage in hospitals (i.e. carbapenems, broad-spectrum cephalosporins, etc.).

As a last resort drug, tigecycline was administrated as a third course of antibiotics in 12% of patients. Tigecycline has not been approved by the US Food and Drug Administration for the treatment of VAP [14]; notwithstanding this, its pharmacological and microbiological profile prompted physicians' use of the drug in other infections caused by MDR pathogens featuring limited therapeutic options [15].

The crude mortality rate in our study was 49%. Although other series of critically ill patients with confirmed 2009 influenza A (H1N1) infection have shown smaller percentage (i.e. 14-28% [16,17]), Heyland *et al.* [18] reported that in patients with VAP the mortality rate can be increased to 76% if the infection is caused by MDR pathogens.

Interestingly, there were no significant differences between patients with and without VAP and between patients with bacteriemic and non-bacteriemic VAP, in terms of demographic characteristics, APACHE II and SOFA scores, prevalence of risk factors for influenza disease, duration of the MV, LOS, clinical success and mortality rate (*Table 1*). Our small sample size may have biased this observation.

In summary, we have demonstrated that VAP was a common complication among our patients with confirmed 2009 influenza A (H1N1) and required invasive respiratory support. In the Latin American scenario of high rates of infections due to resistant microorganisms these patients received several courses of broad spectrum antibiotics associated with the selection and emergence of MDR pathogens (i.e. carbapenems, vancomycin).

From this particular point of view we should consider the 2009 influenza A (H1N1) outbreak as a challenge for our hospital infection control and antimicrobial stewardship programs.

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