Co-infection in severe influenza: a new epidemiology?

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In 2009, a novel influenza A (H1N1) virus emerged in Mexico and caused human infection, including severe pneumonia in young and previously healthy adults [1]. Since 2009, the virus has continued to circulate, causing cases of viral pneumonia and acute respiratory distress syndrome requiring intensive care unit (ICU) admission. Other serotypes (influenza B, A (H3N2)) circulate concomitantly and are also responsible for cases of severe acute illness requiring ICU admission [2]. Although primary viral pneumonia may evolve towards acute respiratory distress syndrome and death, bacterial co-infection is frequently described in these cases, may contribute to the development of ARDS and respiratory failure, and is clearly associated with higher mortality [1, 3].

In this issue of Intensive Care Medicine, Martin-Loeches et al. studied 2,901 patients with influenza infection hospitalized in 148 Spanish ICUs from 2009 to 2015 and found that 16.6% of them had microbiologically confirmed community-acquired co-infection (i.e. co-infection diagnosed within the first 2 days of hospital admission) [4]. Similar to previously

reported data from this group [5], *Streptococcus pneumoniae* was the predominant pathogen recovered, followed by *Pseudomonas aeruginosa* and methicillin-susceptible *Staphylococcus aureus* (MSSA). Not unexpectedly, data from the United States found that *Staphylococcus aureus* was the predominant organism, with a higher prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) [6] . Interestingly, the authors found an apparent increased rate of co-infection over time (from 11.4% in 2009 to 23.4% in 2015), without clear explanation. A recent meta-analysis showed that co-infection rates ranged from 2% to 65% [7]. This difference between studies could be explained by differences in methods of sampling, timing of samples, pre-hospital antibiotic administration and different definitions of co-infection (i.e. whether or not it was microbiologically confirmed, etc…). In the study by Martin-Loeches et al., it is difficult to draw conclusions on the exact incidence of co-infection and its increase over time: firstly, the definition of co-infection required laboratory confirmation and the study didn't record the proportion of patients having received antimicrobials before hospital admission (which would decrease the ability to confirm co-infection in the laboratory and can vary over time); and secondly, due to the use of non-invasive techniques, namely tracheal aspirate, for diagnosing pneumonia, authors might have missed some cases that would only be laboratory confirmed by more invasive sampling (i.e. bronchoscopy). Furthermore, they could have classified patients as having co-infection whereas they were only colonized [8]. This potential overestimation could also explain the high rate of *P. aeruginosa* co-infection observed in that study (14.1%): in another recent study in patients with influenza-related infection, authors found a 1.3% rate of *P. aeruginosa* co-infection in patients with CAP and 8.3% in patients with healthcare associated pneumonia (HCAP) [9]. The high incidence found in the present study cannot be explained by a local (national) feature, since same authors reported lower rates of *P. aeruginosa* CAP and HCAP in Spain during this same time [10, 11]. Either false positives (patients diagnosed as

pneumonia whereas only colonized) or a specific, not yet described, influenza–*P. aeruginosa* co-infection (Shah et al. found similar incidence of *P. aeruginosa* [12]) could explain such high rates of *P. aeruginosa* pneumonia, especially if they truly are community acquired. The high rate of co-infection due to *Aspergillus* (7.2%) is also surprising: although invasive pulmonary aspergillosis has been described in patients with H1N1-related pneumonia, it has rarely been described as a community-acquired co-infection but more as a secondary fungal infection, even in immunosuppressed patients [13, 14]. Although this study focused on community-acquired co-infection (and in fact excluded patients admitted from nursing homes or other healthcare facilities), the high incidences of *P. aeruginosa* and *Aspergillus* as pathogens responsible for co-infection speak in favour of a mix of community-acquired infections and secondary bacterial and fungal infections.

Another surprising result of this paper is the absence of association between appropriate use of antibiotics and mortality, since this has been demonstrated years ago [15]. However, this could be explained not (only) by an unknown and complex host-pathogen interaction, as stated by the authors, but by the high reported rate of inappropriate empiric therapy (>15%) that was similar in survivors and non-survivors [4]. The particular epidemiology of pathogens responsible for co-infection, specifically the higher than expected rates of *P. aeruginosa* and *Aspergillus*, may explain this finding.

Some important messages should be taken from this paper, as the winter is near in the northern hemisphere and we will soon probably face new cases of influenza-related illness requiring ICU admission. First, co-infection is frequent in patients with influenza infection. Physicians taking care of these patients should strongly consider whether their critically ill influenza patient may be co-infected, and empirically treat with antibiotics. Second, co-infection is associated with higher mortality rate than primary viral infection. Although this was previously demonstrated in several studies, this is the largest study published to date that

confirms this association. Rice et al. found, in 2012, that among 683 patients with influenza A H1N1 infection, bacterial co-infection was frequent (30.3%) and associated with higher mortality rate as compared to patients without [6]. In a more recent study on 507 ICU patients, Shah et al. found a 22.5% rate of bacterial co-infection and a similar association between bacterial co-infection and death [12]. It is highly probable that the mechanism explaining the higher mortality is due to either to the bacterial infection itself, or to an association of virulence factors from both virus and bacteria. And lastly, as shown in this paper and others, the epidemiology of pathogens responsible for co-infection is regional and likely depends on many local factors, but may also be subject to change over time, with emergence in the community of pathogens usually seen in nosocomial infections [6, 7, 9, 12].

These and previous data on co-infection rates and association with higher mortality beg the question of whether every patient with severe influenza should be treated with antibiotics? Unfortunately this paper doesn't give the answer to this crucial question, but the answer may very well be an emphatic "Yes". Given the high probability of bacterial co-infection in these patients, its association with mortality, and the fact that delaying antimicrobial treatment could be associated with even higher mortality [16], the empiric use of antimicrobial treatment in such patients should be encouraged. Although some biomarkers (and in particular procalcitonin) have been shown to be associated with bacterial co-infection in this setting, their accuracy is not sufficient to determine initiation of antimicrobial treatment [17]. Procalcitonin may be helpful in this setting as a marker to stop antimicrobial treatment in patients without proven infection and/or low procalcitonin level [18]

In summary, clinicians should keep in mind that co-infection is frequent in patients with influenza-related infection requiring ICU admission. Thus, empiric antimicrobial treatment should be started early. The choice of the initial antimicrobial treatment should be made on the local and national epidemiology and target pathogens responsible for CAP: in

France and northern Europe, *S. pneumoniae* and methicillin-susceptible *S. aureus* seem to be the predominant pathogens. In the US, the high incidence of methicillin-resistant *S. aureus* should be taken into account for the initial choice of antibiotics [6]. If *P. aeruginosa* incidence is increasing over time (which remains to be confirmed in further studies), it may also need empiric antimicrobial coverage since it may have an impact on overall mortality.

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