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Coronavirus Disease 2019 (COVID-19):

A critical care perspective beyond China

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Clinical evidence helps to progress in patient-level and population-level decision-making. We need to build on prior experience and identify similarities *versus* differences. In this sense, the pandemic influenza surge in 2009 can be of help. Our colleagues in Wuhan, who placed their lives at risk by treating patients with COVID-19, recently reported their experience in a scenario of crisis management with limited

resources [1]. Interpretation of these findings in comparison with first reports of pandemic influenza in European ICUs would help to better confront the current challenge [2]. Some intensivists are extrapolating influenza A (H1N1)pdm2009 data and applying it to COVID-19, but there is a huge difference between the coronavirus and influenza, with respect to the impact of their viral shedding. In influenza A (H1N1)pdm2009, medical and nursing staff was not dying more often than patients. In SARS and MERS this was the case, and it appears that hospital staff are also particularly vulnerable in COVID-19 [3]. It is likely that some "sick" coronavirus patients shed very large amounts of virus, whereas in influenza that is not necessarily the case. If a healthcare worker is exposed to a large initial inoculum of coronavirus, ARDS can develop rapidly.

To provide useful insight, Table 1 compares the Wuhan report with our experience with the first ICU admissions caused by influenza A (H1N1)pdm2009 [2]. Among 37 ventilated patients in the Wuhan cohort [1], only 4 (10.8%) were alive and free of mechanical ventilation 28-days after ICU admission. In contrast, a first look suggests that 28-day survival rate in the European influenza cohort was more than doubled. This can be due to the delayed intubation (patients admitted in ICU when already under mechanical ventilation or requiring a fraction of inspired oxygen (FiO2) $\geq$ 60%) associated with the extreme working conditions and the limited resources in Wuhan. Indeed, data from a detailed surveillance study from the China CDC indicates that mortality rates in critically ill patients from other Chinese provinces were lower than 50% [3]. This analysis reports that overall, 80% of confirmed cases were mild, 15% of severe cases required hospitalisation and 5% were critically ill. However, as many patients can remain asymptomatic or with very low symptomatology and because criteria of hospital admission were not standardised, the proportion of patients requiring supportive techniques for hypoxemia is probably lower. COVID-19 is showing respiratory deterioration 7-9 days after onset, which is double the 3-5 days period documented in influenza pandemic, suggesting that it cannot be related to the viral load. This interpretation may justify the high rate of use of steroids in the Wuhan report [1]. Despite some controversies, steroids, alpha-interferon and macrolides are not beneficial [4]. Prior experience with viral pneumonia, including influenza and MERS-coronavirus,

suggest that steroids can contribute to higher mortality, increase viral replication with longer periods of viral clearance and more superinfections (including invasive pulmonary aspergillosis, as already reported in the Wuhan cohort) [5,6].

Another difference is that most COVID-19 infected patients were diagnosed with viral pneumonia, whereas acute exacerbations of COPD or bronchospasm or myocarditis were more common in influenza. The effect on epidemiology and presentation is unknown due to its coexistence within the epidemic season of influenza. Because presentation is overlapping, tests for SARS-CoV-2 should be conducted in patients with severe pneumonia of unknown aetiology, concomitantly with the search for other respiratory viruses.

A common aspect with the influenza virus is the tropism for lower respiratory tract and its impact on the interpretation of diagnostic tests [7]. RT-PCR tests can be affected by sampling errors and viral load, with prior studies in SARS demonstrating low sensitivity during the first days after onset. Moreover, multiple RT-PCR tests of throat or nasopharyngeal swabs have been reported as false negative when compared with BAL tests. Its consequent impact on screening of potential organ or tissue donors is the reason why a definition of clinically “suspected cases” of acute respiratory disease was introduced for recording cases in Hubei, and why chest CT for COVID-19 screening is currently conducted in China. Practical implications are that personal protective equipment (PPE) should be used and infection control measures should not be minimised in patients with pneumonia and high clinical suspicion, due to the high risk of spread and contagion of this virus. In intubated patients, a non-bronchoscopic BAL (Combicath ®) specimen should be obtained (rather than a CT scan) in cases with negative RT-PCT upper respiratory tract swabs.

Thin-slice Chest CT findings have been recommended in Hubei, China as a major evidence for clinical diagnosis of COVID-19. Typical CT findings of COVID-19 include peripherally distributed multifocal ground-glass opacities with patchy consolidations and posterior part of lower lobe involvement predilection. Serial CT scans have been used to monitor evolution. Extend and densities of ground-glass opacities indicate disease progression [8]. It is not clear that it would provide better information that monitoring hypoxemia, as a surrogate of severity.

Protecting health care workers and preparedness of ICUs to confront an epidemic cluster should be the main priority, based on experiences learnt from MERS-coronavirus and 2003 SARS coronavirus [8]. Recently, antiseptic hand rubbing using ethanol-based disinfectants was found to be less effective than hand washing in inactivating influenza virus under experimental conditions [9]. For patients with coronavirus suspicion in the ICU, airborne plus contact precautions and eye protection should be implemented. During aerosol-generation procedures, wearing a fit-tested N95 mask in addition to gloves, gown and face/eye protection is recommended. Open suctioning of the respiratory tract, manual ventilation before intubation, nebulizer treatment, and chest compressions were identified as risk procedures during the SARS outbreak [10]. Close-circuit suctioning may reduce exposure to aerosols in intubated patients. Thus, support with early diagnosis, implementation of effective infection control measures, and limitation of procedures associated with risk of environmental and personal contamination, such as aerosolisation, bronchoscopies or transfers for CT scans should be implemented.

Ventilator strategies favouring aerosolisation, such as non-invasive mechanical ventilation (NIV), which may quite delay but not avoid intubation, should be limited, and hypoxemia rescue therapies such as nitric oxide should be implemented. Use of non-invasive ventilation is controversial, showing limited efficacy in MERS and is associated with very high levels of aerosol spread, exposing staff at much greater risk of infection [11, 12]. However, NIV can avoid the need for ventilation, at least in SARS. There is therefore an argument that it may be appropriate only if adequate levels of staff protective equipment are available [13]. In influenza, a small cohort of patients showed that high-flow nasal cannula was associated with avoidance of intubation in 45% of patients, although those with shock or high severity-of-illness required intubation [14]. Thus, efforts should be done not to delay intubation in patients with viral pneumonia and acute respiratory failure.

In summary, it is necessary to go beyond China, as some results and practices may not be generalisable elsewhere. A priority should be to protect healthcare workers from exposure. ICU doctors should participate in early identification and lead the management of these patients.

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Table 1. Baseline characteristics of ICU patients with confirmed acute respiratory illness.

Study	Yang et al., 2020 (1)	Rello et al., 2009 (2)
Illness	SARS-CoV-2 pneumonia	influenza A (H1N1)pdm2009
Total patients with confirmed illness	52	32
Age, mean (SD)	59.7 (13.3)	40 (13.9)
Sex		
Male	35 (67%)	21 (65.6%)
Female	17 (33%)	34.4% (11)
Days from onset symptoms to ICU admission, median (IQR)	9.5 (7–12.5)	3 (2-6)
Days from onset symptoms to diagnosis, median (IQR)	5 (3-7)	2 (1-6)
APACHE II score, mean (SD)	16.7 (1.3)	13.8 (6.4)
SOFA score, mean (SD)	-	7.1 (3.3)
Signs and symptoms*		
Fever	98%	96%
Cough	77%	88%
Dyspnoea	63.5%	-
Malaise	35%	30%
Myalgia	11.5%	69%
Headache	6%	459%
Rhinorrhoea	6%	-
Vomiting	4%	-
Arthralgia	2%)	-
Chest pain	2%	-
Sore throat	-	58%
Sudden onset symptoms	-	46%
Treatment		
Antibacterial agents	49 (94%)	32 (100%)
beta-lactam plus fluoroquinolones	-	20 (62.5%)
beta-lactam plus macrolides	-	6 (18.7%)
beta-lactam plus linezolid	-	5 (15.6%)
levofloxacin as monotherapy	-	1 (3.1%)
Steroids	30 (58%)	11 (34.4%)
MV		
Invasive	37 (71%)	24 (75%)
Non-invasive	22 (42%)	16 (66.6%)
	29 (56%)	8 (33.3%)
HFNC	33 (63.5%)	-
Immunoglobulin	28 (54%)	-
Antiviral agents		
Oseltamivir standard dose (75mg twice/daily)	23 (44%) 18 (35%)	21 (65.6%) 32 (100%)
Oseltamivir high dose (150mg twice/daily)	-	10 (31.2%)
Ganiciclovir	14 (27%)	-
Lopinavir	7 (13.5%)	-
Vasoconstrictive agents	18 (35%)	20 (62.5%)
Renal replacement therapy	9 (17%)	7 (21.9%)
Prone position ventilation	6 (11.5%)	8 (33%)
ECMO	6 (11.5%)	Not implemented
Comorbidities / Complications	ARDS: 35 (67%) Hyperglycaemia: 18 (35%) Acute kidney injury: 15 (29%) Liver dysfunction: 15 (29%) Cardiac injury: 12 (23%) HAP: 7 (13.5%) Gastrointestinal haemorrhage: 2 (4%) Pneumothorax: 1 (2%) Bacteraemia: 1 (2%) Urinary tract infection: 1 (2%)	Obesity: 10 (31.3%) BMI 30 to 40: 6 (18.7%) Asthma: 5 (15.6%) BMI>40: 4 (12.5%) COPD: 4 (12.5%) Pregnancy: 2 (6.3%) Heart failure: 1 (3.1%) Arterial hypertension: 1 (3.1%) Chronic renal failure: 1 (3.1%) Diabetes mellitus: 1 (3.1%) HIV: 1 (3.1%) Neuromuscular disease: 1 (3.1%) Hematologic disease: 1 (3.1%)

Pathogens identified		
Pseudomonas aeruginosa	1 (2%)	3 (9.3%)
Aspergillus flavus	1 (2%)	1 (3.1%)
Aspegillus.fumigates	1 (2%)	-
	1 (2%)	-
Klebsiella pneumoniae	1 (2%)	-
Serratia marcescens	1 (2%)	-
Invasive candidiasis		
Overall 28-day Mortality	32 (61.5%)	16 (30.8%)
Length of MV for survivors, median (IQR)	-	10 (1-21)

**Rello et al., reported signs and symptoms from a total of 735 cases of influenza A (H1N1)v were confirmed in Spain in 2009.*

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD: standard desviation; IQR: interquartil range; ICU: intensive care unit; APACHE: acute phsyology and chronic health evaluation II; SOFA: sequential organ failure assessment; MV: mechanical ventilation; HFNC: High flow nasal cannula; ECMO: Extracorporeal membrane oxygenation; ARDS: acute respiratory distress syndrome; HAP: hospital-acquired pneumonia; BMI: body mass index; COPD: chronic obstructive pulmonary disease; HIV: positive human immunodeficiency virus; IMV: invasive mechanical ventilation