Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Authors' contributions

Study design: HZ, BHS, LAC, JH
Data collection: HZ, JT, XZ, AL, LW, WZ
Writing of article: HZ, LAC
Critical revision: XZ, HLH, WM, BHS, JH
Approval of final version: all authors.

Declarations of interest

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Hazardous mismatch between pulmonary pathogens and antibiotic treatments in COVID-19 patients

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Editor—In late December 2019, a new outbreak of pneumonia of unknown origin was described in Wuhan, China,[1] soon ascribed to the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The associated coronavirus disease 2019 (COVID-19) results in respiratory failure in up to 90% of infected patients admitted to the ICU, and manifests with chest CT abnormalities such as ground glass opacities, and multifocal patchy consolidation with or without interstitial changes with a peripheral distribution.[3] Most patients present additional organ dysfunction including acute respiratory distress syndrome (ARDS), septic shock, and cardiac, kidney and hepatic failure. Although there is no current cure for COVID-19, immunomodulatory agents, such as corticosteroids, tocilizumab (anti-interleukin-6 monoclonal antibody), and others have been tested to modulate the cytokine storm that often ensues from this novel viral infection.[4] The main risk factor associated with these agents is the risk of superimposed pulmonary co-infections.

Given that the majority of COVID-19 patients present unspecific respiratory symptoms and chest radiography abnormalities, empirical antibiotic treatments are commonly prescribed before and during hospitalisation.[5] The recent Surviving Sepsis Campaign guidelines on the management of critically ill patients with SARS-CoV-2 infection suggested empiric antimicrobials/antibacterial agents (as a weak recommendation with low-quality of evidence).[6] Inflammatory markers, such as procalcitonin, have been applied for antimicrobial stewardship, yet in COVID-19, inflammatory biomarkers are generally elevated.

Only limited evidence has been published on pulmonary co-infections in COVID-19 patients undergoing mechanical ventilation. Hence, there is urgency to identify causative pathogens in this population to guide appropriate antibiotic therapy while reducing the risk of drug resistance. Herein, we report data from 53 COVID-19 patients admitted to the ICU and on mechanical ventilation in a single-centre study with a median age of 57 (9) yr. Among these, 26 (49%) received empiric antibiotic therapy upon hospital admission. As recommended for patients with community-acquired pneumonia,[7] empirical therapy comprised ceftriaxone plus a macrolide or levofloxacin (in 17 patients, 32%), but also piperacillin-tazobactam, oxacillin, and linezolid (in nine patients, 16%). Moreover, 43 (81%) received steroids, 18 (34%) hydroxychloroquine, and three (6%) humanized monoclonal antibody against the interleukin-6 receptor. Routine tracheal surveillance cultures were obtained after a median of 2 days from tracheal intubation.

Among 53 tracheal aspirates, 16 (30%) were positive and 37 (70%) negative (Table 1). The causative pathogens most commonly found were *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*; in five cases, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were identified. Among 16 patients with a positive tracheal aspirate, nine had not received antimicrobial therapy. Empirical antimicrobial therapy was inappropriate in three of five patients with positive tracheal aspirate for pathogens not susceptible, and was titrated accordingly. Irrespective, antimicrobial therapy was continued in 21 of 37 patients (57%) with negative tracheal aspirates. Upon stratification by microbiological results of the first respiratory sample there was no difference in antimicrobial therapy, use of adjunctive anti-inflammatory therapies, and mortality.

During the 2009 H1N1 influenza pandemic, in ICU patients with a positive influenza test we routinely prescribed a neuraminidase inhibitor and empiric antibiotics against the most common causes of community-acquired pneumonia in our region (third-generation cephalosporin plus macrolide or monotherapy with respiratory fluoroquinolone). Antibiotics were rapidly de-escalated or stopped within 48 h based on the results of the first surveillance tracheal aspirate cultures.

During the early phase of the COVID-19 pandemic, when the incidence of bacterial superinfection was unknown and according to the Surviving Sepsis Campaign on the management of critically ill adults with COVID-19, empirical antibacterial therapy was administered to 49% of patients admitted in our ICU. Two recent studies reported that 70–89% of critically ill patients with COVID-19 received empiric antibiotic therapy.[8,9] However, antimicrobial therapy was not immediately stopped after microbiological results in 57% of patients with negative tracheal surveillance aspirates with an average duration of 5 days.

The clinical confidence to limit antibiotic use after negative microbiological results was influenced by the unknown

Table 1 Clinical features of patients stratified by microbiology results of the first surveillance tracheal aspirate.*

Characteristics	All patients (53)	First positive tracheal aspirate (16)	First negative tracheal aspirate (37)	*p*
Male sex, % (*n*)	87 (46)	94 (15)	84 (31)	0.661
Age, *yr*	57 (51–64)	55 (53–65)	59 (47–62)	0.197
BMI, kg m^{-2}	28 (25–31)	27 (25–29)	28 (25–33)	0.313
SAPS II	33 (28–39)	31 (26–33)	34 (28–40)	0.086
Entry PEEP, cm H_2O	10 (10–12)	12 (10–12)	10 (10–12)	0.207
Entry P_aO_2/FiO_2, mm Hg	113 (89–150)	109 (87–141)	115 (91–151)	0.720
Days between symptoms and ED	7 (4–10)	7 (4–9)	7 (5–10)	0.395
Days between ED and TI	3 (2–6)	5 (3–7)	3 (2–6)	0.447
Days between TI and first TA	2 (1–3)	2 (2–3)	1 (1–2)	0.053
Inpatient antimicrobial therapy, % (*n* pts)	48 (26)	31 (5)	57 (21)	0.135
Therapy with tocilizumab, % (*n* pts)	6 (3)	19 (3)	0	0.024
Therapy with OH-cloroquine, % (*n* pts)	34 (18)	44 (7)	30 (11)	0.358
Steroids, % (*n* pts)	81 (43)	94 (15)	76 (28)	0.250
C-reactive protein (mg/L)	126 (94–140)	138 (117–143)	121 (74–137)	0.132
Procalcitonin (ng/mL)	0.55 (0.18–1.21)	0.52 (0.14–0.9)	0.62 (0.38–1.8)	0.382
ICU length of stay (days)	14 (8–25)	12 (7–25)	14 (9–23)	0.635
ICU mortality, % (*n*)	53 (28)	62 (10)	49 (18)	0.354

ED, emergency department; SAPS II, Simplified Acute Physiology Score; TA, tracheal aspiration TI, tracheal intubation.

* Student's *t*-test or Mann–Whitney rank sum test, as appropriate, were used to analyse continuous variables and the χ^2 or Fisher's exact test, as appropriate, for non-continuous variables. Data are expressed as mean (standard deviation) or median (inter-quartile range) as appropriate. $P<0.05$.

incidence of bacterial superinfections in patients with COVID-19, by the severity of the clinical status of many patients without improvement despite the antiviral therapy, by the possibility that patients were immunocompromised because of immunomodulatory therapy, and by the fact that half of tracheal aspirates was obtained during antibiotic therapy, increasing the diagnostic difficulty.

Our preliminary data suggest that in mechanically ventilated COVID-19 patients undergoing immunomodulatory therapy, tracheal aspirates should be obtained as soon as possible and antibiotic therapy potentially withheld until microbiology results become available, because of the low rate of positive tracheal aspirates. Based on our local conditions, use of empirical broad-spectrum antibacterial drugs was inappropriate in a substantial number of cases, and narrow-spectrum antibiotics would be preferred. For use of broad-spectrum antibiotics, we can infer that de-escalation based on the results of susceptibility tests or negative tracheal aspirates should be applied as early as possible.

Absence of a specific cure, evidence that intensive care surge capabilities were rapidly overwhelmed, clinical suspicion of nosocomial infections, and wide use of immunomodulatory therapy modified our practice and led us to misuse or overuse antibacterial drugs, failing de-escalation irrespective of the culture results. Evidence from our small cohort of patients call for an urgent and comprehensive analysis of pulmonary co-infections in COVID-19 patients admitted to the ICU. In line with these goals, the COVID-19 Critical Care Consortium is currently collaborating with more than 400 ICUs worldwide to characterise secondary bacterial infections associated with SARS-CoV-2 and provide urgent recommendations on appropriate empiric therapies.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Opioids and the COVID-19 pandemic: does chronic opioid use or misuse increase clinical vulnerability?

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Keywords: COVID-19; opioid; opioid misuse; outcome; risk factor; social determinant

Editor—Opioids have predictable analgesic actions and are widely used in many clinical settings, but they also produce unwanted side-effects including respiratory depression, tolerance and are misused. Misuse and poor opioid stewardship in the therapeutic arena are generally accepted as the underlying cause of what we describe as the 'opioid epidemic' or 'opioid crisis'.[1] According to a UK Office for National Statistics report in 2019,[2] there were 139 845 people in contact with drug services during the 2018–19 period; some of these will be opioid dependent, but for many this will not be a single substance misuse. Moreover, a Public Health England (PHE) report suggests 540 000 patients