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.

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Letter to the Editor

Improving antibiotic stewardship in COVID-19: Bacterial co-infection is less common than with influenza

To the editor in chief

In the recent systematic review and meta-analysis by Lansbury et al. only 7% of hospitalised patients with COVID-19 were reported as having evidence of bacterial co-infection, yet >90% received empirical antibiotics[1]. This finding, which has been replicated elsewhere[2], is hardly surprising given the challenges associated with distinguishing bacterial from viral pneumonia and that bacterial coinfection is likely to worsen an already poor prognosis in these patients[3]. Whilst the role of biomarkers such as procalcitonin is being explored, a desire to treat what is treatable is understandable but represents a threat to antibiotic stewardship[4,5]. In their study, Lansbury et al. found that bacterial coinfection was more common for those in intensive care (ICU) (14%, 95% CI 5–26, vs 4%, 95% CI 1–9) but only one study provided data on the timing of infection in relation to admission. Distinguishing between bacterial co-infection acquired *prior to* or *following* ICU admission is essential when developing antibiotic prescribing policies.

Some of the concern over bacterial co-infection in COVID-19 stems from experience with influenza where bacterial co-infection is well-recognised and often the factor precipitating admission to ICU.[6] Experience is growing that the same is not true for COVID-19[7]. Whilst any patient on ICU is vulnerable to nosocomial infection, we observe that- in contrast to influenza- bacterial co-infection at ICU admission is rare.

Table 1 presents microbiologically-confirmed bacterial co-infection findings from a subset of patients enrolled into the ongoing AspiFlu study (www.isrctn.com/ISRCTN51287266). Ventilated adults with confirmed SARS-CoV-2 or influenza infection that had ≥1 respiratory tract sample sent for culture were included in this analysis. Bacterial co-infection was defined as either i) positive urinary antigen test; ii) culture of pathogen from blood/bronchoalveolar lavage (BAL) fluid; or iii) positive endotracheal aspirate culture with suggestive radiology (e.g. focal/ lobar consolidation), neutrophilia and clinician-instigated antibiotic treatment.

In the influenza cohort, early (<48 h hours of ICU admission) bacterial co-infection was common, 14/24 (58%), and caused by community-acquired pathogens such as *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pyogenes* (Group A strep) in 7/14. In contrast, early co-infection was uncommon in the COVID-19 cohort 3/36 (8%, $P<0.0001$). The incidence of late (>48 h of ICU admission) co-infection in COVID-19 did not significantly differ from influenza (36% vs. 50%, $p=0.3$) and in 12/13 cases was caused by gram negative bacteria commonly associated with ventilator-associated pneumonia (VAP) and catheter-related bloodstream infection[1]. Important differences between the groups were that the influenza cohort had a shorter duration of symptoms before ICU admission (5 vs 9 days, $p=0.002$) and a higher proportion received Extra Corporeal Membrane Oxygenation (46% vs 0%, $P<0.0001$) and BAL sampling (79% v 8%, $P<0.0001$). Interestingly, the influenza cohort had better survival despite worse baseline SOFA/APACHE 2 scores.

For the purposes of antibiotic stewardship, COVID-19 is not like influenza. Most patients with COVID-19 present to ICU with a viral pneumonitis rather than bacterial co-infection. More work is needed on strategies and biomarkers to help identify those most likely to benefit from antibiotics. Whilst clinicians must remain vigilant about nosocomial infection, we advocate against routine empiric antibiotic use in patients hospitalised with COVID-19 infection. Courses of empirical antibiotics initiated whilst SARS-CoV-2 test results are pending should be promptly reviewed upon having the diagnosis of COVID-19 confirmed. Antibiotics should only be continued for those with a presentation suggestive of bacterial coinfection (e.g. productive cough, focal consolidation, neutrophilia) or supportive positive microbiology[4]. A narrow spectrum antibiotic should be used wherever possible, informed by local guidance and microbiology results. It can be especially difficult to withhold antibiotics from patients with COVID-19 cytokine release syndrome, which can mimic bacterial sepsis. In such patients, the ongoing need for antibiotics should be continuously reviewed in light of response to immunomodulatory therapy and limited to as short a duration as possible. The impact of immunomodulatory therapies such as corticosteroids (now standard of care for ventilated patients in light of RECOVERY trial findings[8]), anti-cytokine antibodies and JAK inhibitors (currently being investigated[9,10]) on bacterial coinfection warrants further study. Future research could also explore whether the rate of nosocomial infection in ICU patients with COVID-19 was artificially high at the peak of the pandemic when challenging working environments and shortages of PPE may have impeded optimal infection prevention and control practice.

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Table 1
Bacterial co-infection in mechanically ventilated adults with severe viral pneumonia.

	Influenza ($n=24$)		SARS-Cov-2 ($n=36$)		
Patient characteristics					
Age, median (IQR)	56 (47–63)		59 (51–65)		$p=0.29$
Male, n (%)	15 (63%)		25 (69%)		$p=0.59$
Severe immunosuppression, n (%)	2 (8%)		2 (6%)		$P>0.99$
Systemic corticosteroids last 21 days, n (%)	7 (29%)		4 (11%)		$p=0.097$
Chronic Lung Disease, n (%)	7 (29%)		4 (11%)		$p=0.097$
Chronic Kidney Disease, n (%)	1 (4%)		3 (8%)		$p=0.64$
Diabetes, n (%)	4 (17%)		12 (33%)		$p=0.23$
Hypertension, n (%)	5 (21%)		13 (36%)		$p=0.26$
Active / Past Smoker, n (%)	11 (46%)		14 (39%)		$p=0.61$
Duration of symptoms (days), median (IQR)	5 (2–7)		9 (6–11)		$p=0.0018$
Admission SOFA score, median (IQR)	10 (9–13)		6 (4–8)		$p<0.0001$
Admission APACHE 2 score, median (IQR)	22 (17–27)		14 (11–19)		$p<0.0001$
Lymphocyte: Neutrophil ratio, median (IQR)	112 (7–20)		13 (6–18)		$p=0.85$
Diagnostic sampling, no of patients (%)					
Respiratory tract sampling	24 (100%)		36 (100%)		$p>0.99$
Bronchoalveolar lavage	19 (79%)		3 (8%)		$P<0.0001$
Urine legionella Antigen	19 (79%)		30 (83%)		$p=0.74$
Urine pneumococcal Antigen	20 (83%)		27 (75%)		$p=0.53$
Blood culture	24 (100%)		36 (100%)		$p>0.99$
Mycoplasma serology/PCR	20 (83%)		7 (19%)		$P<0.0001$
Interventions and Outcomes					
Renal replacement therapy, n (%)	15 (63%)		15 (42%)		$p=0.19$
Extra Corporeal Membrane Oxygenation, n (%)	11 (46%)		0 (0%)		$P<0.0001$
Days ventilated, median (IQR)	16 (9–28)		18 (12–27)		$p=0.62$
Days on ICU, median (IQR)	22 (16–32)		20 (16–31)		$p=0.97$
90 day all-cause mortality, n (%)	4 (17%)		18 (50%)		$p=0.013$
Bacterial coinfection					
Early (<48 h of ICU admission), n (%)	14 (58%)		3 (8%)		$P<0.0001$
Late (>48 h of ICU admission), n (%)	12 (50%)		13 (36%)		$p=0.30$
Gram positive	Early	Late	Early	Late	
Streptococcus pneumoniae	2	0	0	0	
Staphylococcus aureus	2	0	1	1	
Streptococcus pyogenes (Group A Strep)	2	0	0	0	
Enterococci	0	1	1	0	
Gram negative	Early	Late	Early	Late	
Haemophilus influenzae	1	1	0	0	
Coliforms	1	5	0	9	
Pseudomonas	1	1	0	1	
Other	5	4	1	2	

Influenza; A not subtyped ($n=9$), H1N1 ($n=10$), H3N2 ($n=4$), B ($n=1$). *Coliforms; Klebsiella*, *Escherichia coli*, *Citrobacter*, *Enterobacter*, *Serratia*. *Other; Proteus*, *Stenotrophomonas*, polymicrobial. *Respiratory tract sampling;* sputum, bronchoalveolar lavage, non-directed lavage, endotracheal aspirate. p values calculated using Fisher's exact test for categorical and Mann-Whitney U test for continuous variables using GraphPad Prism 8.4.2. SOFA/Apache 2 scores calculated using www.mdcalc.com.

Conflict of Interest

None.

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