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

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1 **Title Page**

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1 TO THE EDITOR IN CHIEF - In the recent systematic review and meta-analysis by Lansbury et al. only 7% of
2 hospitalised patients with COVID-19 were reported as having evidence of bacterial co-infection, yet >90% received
3 empirical antibiotics¹. This finding, which has been replicated elsewhere², is hardly surprising given the challenges
4 associated with distinguishing bacterial from viral pneumonia and that bacterial coinfection is likely to worsen an
5 already poor prognosis in these patients³. Whilst the role of biomarkers such as procalcitonin is being explored, a
6 desire to treat what is treatable is understandable but represents a threat to antibiotic stewardship^{4,5}. In their
7 study, Lansbury et al. found that bacterial coinfection was more common for those in intensive care (ICU) (14%,
8 95% CI 5-26, vs 4%, 95% CI 1-9) but only one study provided data on the timing of infection in relation to
9 admission. Distinguishing between bacterial co-infection acquired *prior to* or *following* ICU admission is essential
10 when developing antibiotic prescribing policies.

11
12 Some of the concern over bacterial co-infection in COVID-19 stems from experience with influenza where
13 bacterial co-infection is well-recognised and often the factor precipitating admission to ICU.⁶ Experience is
14 growing that the same is not true for COVID-19⁷. Whilst any patient on ICU is vulnerable to nosocomial infection,
15 we observe that- in contrast to influenza- bacterial co-infection at ICU admission is rare.

16
17 Table 1 presents microbiologically-confirmed bacterial co-infection findings from a subset of patients enrolled
18 into the ongoing AspiFlu study (www.isrctn.com/ISRCTN51287266). Ventilated adults with confirmed SARS-CoV-
19 2 or influenza infection that had >1 respiratory tract sample sent for culture were included in this analysis.
20 Bacterial co-infection was defined as either i) positive urinary antigen test; ii) culture of pathogen from
21 blood/bronchoalveolar lavage (BAL) fluid; or iii) positive endotracheal aspirate culture with suggestive
22 radiology(e.g. focal/ lobar consolidation), neutrophilia and clinician-instigated antibiotic treatment.

23
24 In the influenza cohort, early (<48h hours of ICU admission) bacterial co-infection was common, 14/24 (58%), and
25 caused by community-acquired pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus*,
26 *Haemophilus influenzae* and *Streptococcus pyogenes* (Group A strep) in 7/14. In contrast, early co-infection was
27 uncommon in the COVID-19 cohort 3/36 (8%, P<0.0001). The incidence of late (>48h of ICU admission) co-
28 infection in COVID-19 did not significantly differ from influenza (36% vs. 50%, p=0.3) and in 12/13 cases was

29 caused by gram negative bacteria commonly associated with ventilator-associated pneumonia (VAP) and
30 catheter-related bloodstream infection¹. Important differences between the groups were that the influenza
31 cohort had a shorter duration of symptoms before ICU admission (5 vs 9 days, p=0.002) and a higher proportion
32 received Extra Corporeal Membrane Oxygenation (46% vs 0%, P<0.0001) and BAL sampling (79% v 8%, P<0.0001).
33 Interestingly, the influenza cohort had better survival despite worse baseline SOFA/APACHE 2 scores.

34

35 For the purposes of antibiotic stewardship, COVID-19 is not like influenza. Most patients with COVID-19 present
36 to ICU with a viral pneumonitis rather than bacterial co-infection. More work is needed on strategies and
37 biomarkers to help identify those most likely to benefit from antibiotics. Whilst clinicians must remain vigilant
38 about nosocomial infection, we advocate against routine empiric antibiotic use in patients hospitalised with
39 COVID-19 infection. Courses of empirical antibiotics initiated whilst SARS-CoV-2 test results are pending should
40 be promptly reviewed upon having the diagnosis of COVID-19 confirmed. Antibiotics should only be continued for
41 those with a presentation suggestive of bacterial coinfection (e.g. productive cough, focal consolidation,
42 neutrophilia) or supportive positive microbiology.⁴ A narrow spectrum antibiotic should be used wherever
43 possible, informed by local guidance and microbiology results. It can be especially difficult to withhold antibiotics
44 from patients with COVID-19 cytokine release syndrome, which can mimic bacterial sepsis. In such patients, the
45 ongoing need for antibiotics should be continuously reviewed in light of response to immunomodulatory therapy
46 and limited to as short a duration as possible. The impact of immunomodulatory therapies such as corticosteroids
47 (now standard of care for ventilated patients in light of RECOVERY trial findings⁸), anti-cytokine antibodies and
48 JAK inhibitors (currently being investigated^{9,10}) on bacterial coinfection warrants further study. Future research
49 could also explore whether the rate of nosocomial infection in ICU patients with COVID-19 was artificially high at
50 the peak of the pandemic when challenging working environments and shortages of PPE may have impeded
51 optimal infection prevention and control practice.

52

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55 clinical staff who worked so tirelessly during the peak of the COVID-19 pandemic.

56

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60

61 **Conflicts of interest**

62 None to declare

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65 **References**

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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				
	14	3		
Early (<48h of ICU admission), n (%)	(58%)	(8%)	P<0.0001	
	12	13		
Late (>48h of ICU admission), n (%)	(50%)	(36%)	p=0.30	
Gram positive				
	Early	Late	Early	Late
<i>Streptococcus pneumoniae</i>	2	0	0	0
<i>Staphylococcus aureus</i>	2	0	1	1
<i>Streptococcus pyogenes</i> (Group A Strep)	2	0	0	0
<i>Enterococci</i>	0	1	1	0
Gram negative				
	Early	Late	Early	Late
<i>Haemophilus influenzae</i>	1	1	0	0
<i>Coliforms</i>	1	5	0	9
<i>Pseudomonas</i>	1	1	0	1
<i>Other</i>	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.

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