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

Risk factors associated with bloodstream infections among critically ill patients with COVID-19

Dear editor,

The understanding and management of COVID-19 among hospitalised patients has evolved with increased use of dexamethasone and Tocilizumab. The ability of dexamethasone and Tocilizumab to dampen the excessive host inflammatory response to SARS-CoV-2 may be associated with improved mortality.[1,2] However, an increase in the incidence of secondary infections associated with these treatments is of concern. In this Journal, Lansbury and colleagues recently reviewed the occurrence of co-infections amongst patients with COVID-19.[3] We sought to evaluate risk factors associated with the development of bloodstream infection (BSI) among critically ill patients with COVID-19.

Patients aged ≥18 years admitted to University College London Hospitals with a positive real-time reverse transcription–polymerase chain reaction (rRT-PCR) test for SARS-CoV-2 RNA between March 2020 and 1st February 2021 were included. The UK has to date experienced two major waves of COVID-19 infections, the first in March-August 2020 and the second in September 2020- March 2021. Ethical approval was granted by the London-Westminster Research Ethics Committee, the Health Research Authority and Health and Care Research Wales (HCRW) on 2nd July 2020 (REC reference 20/HRA/2505, IRAS ID 284,088).

Patient demographics, clinical data, blood culture results, treatments and outcome were recorded from electronic healthcare records on a standardized data collection form. Dexamethasone was prescribed on hospital admission at 6 mg daily for 10 days. Tocilizumab was administered when patients progressed to requiring advanced respiratory support (high flow nasal oxygen, non-invasive ventilation, or invasive ventilation), as a single dose of 8 mg/kg (up to a maximum dose of 800 mg). Blood culture contaminants were defined as those not considered clinically significant at the time and did not require a clinical intervention.

Continuous and categorical variables are reported as median (interquartile range) and n (%), respectively. Comparison of non-parametric continuous data between groups was performed using the Mann Whitney U test. Categorical data were compared using the chi-square test. Binary logistic regression was used to ascertain independent risk factors associated with BSI. Graphs were constructed, and statistical analysis performed using Prism 9.0 (GraphPad Software, La Jolla, CA, USA) and SPSS version 24.0 (IBM Corp).

A total of 404 patients were included (**Table 1**), The median age of patients was 61 (51–69) years, 270 (67%) patients were male, 160 (40%) were admitted in the first surge, and 190 (47%) died in hospital. 102 patients (25%) received dexamethasone alone of who 53 patients (52%) died. An additional 45 patients (11%) received Tocilizumab in addition to dexamethasone of whom 22 (49%) died. No patients received Tocilizumab without dexamethasone.

Of the 404 patients with COVID-19, 76 (18.8%) patients had a clinically relevant positive blood culture (Table 1), most commonly a coagulase negative staphylococcus. The median time from hospital admission to BSI was 18 (11–26) days. Among the 76 patients who had a BSI, six (8%) had more than one organism isolated. The proportion of patients who died was similar between those with and without a BSI ($p = 0.202$).

Factors associated with BSI on univariate analysis included longer duration of follow up time ($p < 0.001$), being admitted in the second surge ($p = 0.038$), requirement for mechanical ventilation ($p < 0.001$), dexamethasone use ($p = 0.006$), and being transferred from another center to ours ($p = 0.002$). On correcting for follow up time, surge, mechanical ventilation, dexamethasone use, and age, mechanical ventilation (OR=2.1(1.1–3.9); $p = 0.028$), longer follow up time (OR=1.013 (1.005–1.022); $p = 0.002$), and younger age (OR=0.979 (0.968–0.990); $p < 0.001$) were associated with a bacteraemia. Dexamethasone and Tocilizumab use were not independently associated with BSI.

We report independent risk factors associated with the incidence of BSI in a critically ill patient cohort with COVID-19. Dexamethasone and Tocilizumab were not independently associated with BSI among critically ill patients with COVID-19. Similar findings have been reported among hospitalised patients with COVID-19, including non- critically ill.[4] Additionally, we found that the occurrence of a BSI was not associated with greater mortality on unadjusted analysis, consistent with findings from a UK national study.[5]

Unsurprisingly, the longer duration of stay on ICU the greater the risk of developing a bacteremia; the latter being a time- dependent covariate. Invasive mechanical ventilation was also associated with a bacteremia, this may reflect greater illness severity which is associated with immune dysregulation in COVID-19.[6,7] Following the initial infectious insult and an associated hyperinflammatory state, a hypoinflammatory state with impaired ability to overcome secondary infections ensues during prolonged critical illness.[8] The time to develop a secondary infection was between 2 and 3 weeks; similar to other reports.[4,9] Younger age being associated with BSI is intriguing, and may reflect increased investigations among patients who appear more likely to have a favorable prognosis; including younger patients and those with fewer co-morbid illness.

At the doses used, dexamethasone and Tocilizumab may not be associated with excessive immune suppression and increased risk of BSI. However, dexamethasone and Tocilizumab attenuate clinical features associated with bacteremia, including an elevated temperature and CRP. We cannot therefore exclude the possibility of occult bacteremia which was undiagnosed. This is of greater concern closer to the time of receiving dexamethasone or tocilizumab, which suppress CRP and temperature for a number of days following administration.[9].

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Table 1
Characteristics and treatment administered to critically ill COVID-19 patients with and without bloodstream infections.

	No positive blood cultures	Positive blood cultures	*p*-value
	328	76	
BMI	28 (24–33)	28 (24–33)	0.790
Age	62 (52–70)	60 (49–67)	0.104
Symptoms to hospital (days)	7 (5–10)	7 (4–10)	0.611
Follow up time (days)	20 (13–32)	41 (22–60)	<0.001
Sex (Male)	205 (67%)	56 (74%)	0.277
Diabetes mellitus	89 (29%)	29 (39%)	0.120
Surge 1	128 (42%)	22 (29%)	0.038
IMV	196 (64%)	69 (91%)	<0.001
Dexamethasone use	158 (52%)	53 (70%)	0.006
Tocilizumab use	31 (10%)	9 (12%)	0.669
Transfer from another hospital	124 (41%)	46 (61%)	0.002
Continuous positive airway pressure use	248 (81%)	59 (78%)	0.468
Cancer	34 (11%)	8 (8%)	0.417
Immunosuppression	37 (12%)	6 (8%)	0.300
Hospital mortality	145 (47.5%)	40 (52.6%)	0.427

As with all retrospective analyses, we acknowledge the possibility of residual confounding, and that results are associative. The small number of patients included also warrants caution in interpreting the findings. There were no predefined criteria for obtaining blood cultures, and we have focused on positive bacteremia rates, but not infectious complications without an associated bacteremia.

In summary, dexamethasone and Tocilizumab were not associated with increased risk of BSI in critically ill patients with COVID-19. Further prospective work investigating particular at-risk subgroups, and the use of diagnostics with greater sensitivity are warranted.

Declaration of Competing Interest

The authors have no competing interest to declare.

Ethical approval

Ethical approval was granted by the London-Westminster Research Ethics Committee, the Health Research Authority and Health and Care Research Wales (HCRW) on 2nd July 2020 (REC reference 20/HRA/2505, IRAS ID 284,088).

CRediT authorship contribution statement

Tim McMillan: Data curation. **Conor Jones:** Data curation. **Cavan J O'Connor:** Data curation, Project administration, Writing – review & editing. **Daniel Nolan:** Data curation. **Jayne Ellis:** Data curation, Writing – review & editing. **Clare Thakker:** Data curation, Writing – review & editing. **Katharina Kranzer:** Data curation, Writing – review & editing. **Neil RH Stone:** Data curation, Writing – review & editing. **Mervyn Singer:** Writing – review & editing, Supervision. **A Peter R Wilson:** Conceptualization, Methodology, Validation, Resources, Data curation, Writing – review & editing, Supervision, Project administration. **Nishkantha Arulkumaran:** Conceptualization, Methodology, Validation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

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Tim McMillan[1], Conor Jones[1]
Division of Medicine, Bloomsbury Institute for Intensive Care Medicine, University College London, Cruciform Building, Gower St, London WC1E 6BT, United Kingdom

Cavan J O'Connor
Department of Clinical Microbiology, University College London NHS Foundation Trust, London, United Kingdom

Daniel Nolan
Division of Medicine, Bloomsbury Institute for Intensive Care Medicine, University College London, Cruciform Building, Gower St, London WC1E 6BT, United Kingdom

Xin Hui S Chan, Jayne Ellis, Clare Thakker, Katharina Kranzer, Neil RH Stone
Department of Clinical Microbiology, University College London NHS Foundation Trust, London, United Kingdom

Mervyn Singer
Division of Medicine, Bloomsbury Institute for Intensive Care Medicine, University College London, Cruciform Building, Gower St, London WC1E 6BT, United Kingdom

A Peter R Wilson
Department of Clinical Microbiology, University College London NHS Foundation Trust, London, United Kingdom

Nishkantha Arulkumaran*
Division of Medicine, Bloomsbury Institute for Intensive Care Medicine, University College London, Cruciform Building, Gower St, London WC1E 6BT, United Kingdom

*Corresponding author.
E-mail addresses: nisharulkumaran@doctors.org.uk, nish.arulkumaran@nhs.net (N. Arulkumaran)
[1] These authors contributed equally to this work.