Abstract S53 Figure 1 Rates of mortality against cumulative number of antibiotics received per patient during inpatient spell.

associated with increased inpatient mortality in both the first wave (54.1% mortality for ≥ 1 antibiotic vs 19.0% receiving no antibiotic, $p < 0.00001$) and second wave (25.2% mortality for ≥ 1 antibiotic vs 4.3% receiving no antibiotic, $p < 0.00001$). Successive numbers of antibiotics related to progressive worsening of mortality rates in both waves (OR 1.453, $p < 0.0001$). Antibiotic use was also associated with prolonged length-of-stay in the first wave (13.0 ± 13.4 days for ≥ 1 antibiotic vs 6.9 ± 12.1 receiving no antibiotic, $p = 0.0011$) and second wave (11.9 ± 11.7 days for ≥ 1 antibiotic vs 6.6 ± 10.6 receiving no antibiotic, $p = 0.00005$).

Conclusion In both COVID-19 waves, antibiotic administration correlated to increased inpatient morbidity and mortality. Given a near-linear relationship of mortality and cumulative antibiotic numbers, antimicrobial stewardship is essential, and tapering an appropriate therapy for likely responsible pathogens will yield lower mortality compared to overlapping coverage and inappropriate escalation. We strongly discourage the use of empirical antibiotics without supporting biochemical evidence of bacterial co-infection for possible future COVID-19 waves.

REFERENCE

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Understanding COVID-19 mechanisms

S54 ELEVATED NETOSIS AND MIGRATION BUT IMPAIRED ANTI-MICROBIAL RESPONSES IN NEUTROPHILS FROM NON-ICU, HOSPITALIZED COVID-19 PATIENTS

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Rational Infection with the SARS-CoV2 virus is associated with elevated neutrophil counts. Evidence of neutrophil dysfunction in COVID-19 is based predominantly on transcriptomics or single functional assays. Cell functions are interwoven pathways, and so understanding the effect of COVID-19 across the spectrum of neutrophil function may identify therapeutic targets to treat disease.

Objectives Examine neutrophil phenotype and functional capacity in COVID-19 patients versus age-matched controls (AMC).

Methods Isolated neutrophils from 41 non-ICU COVID-19 patients and 23 AMC underwent *ex vivo* analyses for migration, phagocytosis of *Streptococcus pneumoniae*, reactive oxygen species (ROS) generation, neutrophil extracellular trap formation (NETosis) and cell surface receptor expression. Serum DNase 1 activity was measured, alongside circulating levels of cell-free (cf)DNA, myeloperoxidase (MPO), VEGF, IL-6 and sTNFRI. All measurements were correlated to clinical outcome. Serial sampling on day 3–5 post hospitalisation were also measured.

Results Compared to AMC, COVID-19 neutrophils demonstrated elevated transmigration ($p = 0.0397$) and NETosis ($p = 0.0366$), but impaired phagocytosis ($p = 0.0236$) associated with impaired ROS generation ($p < 0.0001$). Surface expression of CD54 ($p < 0.0001$) and CD11c ($p = 0.0008$) was significantly increased and CD11b significantly decreased ($p = 0.0229$) on COVID-19 patient neutrophils. On day 3–5 follow-up, levels of senescent neutrophils increased compared to day 1 (indicated by decreased CXCR2 and elevated CXCR4 expression ($p = 0.0332$)). COVID-19 patients showed increased systemic markers of NETosis including increased cfDNA ($p = 0.0153$) and impaired DNase activity ($p < 0.001$). MPO, VEGF, sTNFRI, and IL-6 ($p < 0.001$) were elevated in COVID-19, which positively correlated with disease severity by 4C score.

Conclusion COVID-19 is associated with neutrophil dysfunction across all main effector functions, with altered phenotype, elevated migration, impaired antimicrobial responses and elevated NETosis. These changes represent a clear mechanism for tissue damage and highlight that targeting neutrophil function may help modulate COVID-19 severity.

Please refer to page A189 for declarations of interest related to this abstract.

S55 PERSISTENT CHANGES TO THE NASAL CILIATED EPITHELIUM FOLLOWING SARS-COV2 INFECTION: A LONGITUDINAL COHORT ANALYSIS FROM FOLLOW-UP COVID

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Background SARS-CoV2 binds to the respiratory epithelium. Little is known about the recovery and regeneration of the epithelium following COVID-19. Poor recovery could leave individuals at risk of secondary bacterial infection and persistent symptoms.

The aim of this study was to assess epithelial recovery following SARS-CoV2 infection across a range of acute illness severities.

Methods 41 people were recruited at 3–12 months post PCR confirmed SARS-CoV2 infection. The respiratory epithelium was sampled by brushing the nasal inferior turbinate. Ciliary function was assessed by high-speed video microscopy and ultrastructure was assessed by electron microscopy. A subset of patients had repeat nasal brushing 3–5 months following their first visit. Demographics, severity of infection and longitudinal symptoms were recorded for comparison. Results were compared to healthy controls and historical controls recruited prior to the pandemic.

Results Post-COVID epithelium was friable and most samples contained detached single cells and blood. Epithelial disruption

Abstract S55 Figure 1 Transmission Electron Micrographs of ciliated epithelial cells 3 months- 1 year post-COVID. Red circles represent microtubular subunits assembling during ciliogenesis, the white arrow shows short regenerating cilia. Yellow boxes surround intracytoplasmic cilia seen in 90% post COVID cases and suggestive of a defect in ciliogenesis

score was 3.0 ± 0.6 compared to 2.4 ± 0.6 for controls ($p < 0.01$). Percentage of goblet cells in post-COVID patients and controls was similar, but there was a significant lack of ciliation of the epithelium post-COVID ($p < 0.01$). No significant improvement was seen in 14 patients with a second sampling point 3–5 months later. Ultrastructural analysis revealed evidence of regeneration of ciliated epithelial cells such as the presence of microtubular subunits and basal bodies in the cytoplasm as well as shortened cilia (figure 1).

Ciliary beat amplitude per second was significantly reduced compared to controls ($60.2 \pm 19.2 \mu\text{m/s}$ vs $78.5 \pm 8.9 \mu\text{m/s}$) ($p < 0.0001$). 29% individuals post-COVID had some rotating cilia, usually a specific sign for Primary Ciliary Dyskinesia. Ultrastructural analysis revealed 17% ($\pm 11\%$) cilia had defects, these included defects of the central pair of microtubules, in keeping with a rotational beat pattern. 90% cases had cells with intracytoplasmic cilia, suggestive of epithelial

inflammation and dysfunctional ciliogenesis. This was seen in $< 1\%$ controls.

No significant difference was seen between community, hospitalised, or critical care cases.

Conclusion Epithelial disruption and defects in epithelial regeneration persist for up to 1 year post infection with SARS-CoV-2, irrespective of initial illness severity. Persisting inflammation, or a failure of repair, are possible pathological processes for further exploration.

S56

MEASURES OF INFLAMMATION, COMPLEMENT ACTIVATION AND COAGULATION IN PATIENTS WITH COVID-19

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Introduction Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has resulted in a global pandemic of unprecedented magnitude causing a disease that varies widely in nature and severity ranging from asymptomatic carriers to life-threatening illness requiring ICU support. Excessive immune activation is believed to underpin the pathophysiology, however, despite the identification of treatments which target this (Dexamethasone, Tocilizumab) there remains significant morbidity and mortality suggesting other pathobiological mechanisms are at play including the complement cascade.

Methods We compared the clinical, physiological & biological characteristics including levels of inflammation, complement activation and coagulation of 52 patients with confirmed or clinically suspected COVID-19, stratified based on their degree of respiratory failure (Mild: $\text{FiO}_2 \leq 0.4$; Moderate: $\text{FiO}_2 > 0.4 \pm \text{NIV}$ support (HFNO/CPAP) or Severe: mechanical ventilation) and compared to 20 age and co-morbidity matched

Abstract S56 Table 1 Table to show measures of complement activation, inflammation and coagulation in patients with COVID-19 stratified by disease severity

	Mild	Moderate	Severe	Overall P-Value	Mild vs Mod*	Mild vs Sev*	Mod vs Sev*
Number (%)	30	28	9	-	-	-	-
CRP (mg/L)	75.5 [28.5,117.25]	93.5 [72,143.5]	60 [34,157.5]	NS	NS	NS	NS
Ferritin (ug/L)	426 [290.5,847.5]	728 [381.25,1071.5]	857 [443,1607.5]	NS	NS	NS	NS
PCT (ug/L)	0.08 [0.06,0.19]	0.16 [0.09,0.49]	0.19 [0.12,0.8]	0.019	NS	0.046	NS
LDH (U/L)	708.5 [523.5,903]	830 [569,1122]	1037 [927.5,1086]	0.008	NS	0.006	NS
Platelets ($10^9/\text{L}$)	220 [174.75,328.75]	255 [203.5, 335]	292 [209.5, 329.5]	NS	NS	NS	NS
INR	1.1 [1.08,1.23]	1.1 [1.1, 1.2]	1.1 [1.1, 1.15]	NS	NS	NS	NS
APTR	0.9 [0.9,1.0]	0.9 [0.9, 1.0]	1.0 [0.95, 1.10]	NS	NS	NS	0.038
D-dimer (ugFEU/ml)	0.56 [0.38,0.95]	0.74 [0.55, 1.52]	0.85 [0.54, 19.2]	NS	NS	NS	NS
Fibrinogen (g/L)	4.45 [4.05,5.22]	4.7 [4.3, 6.38]	4.3 [3.9, 6.0]	NS	NS	NS	NS
Thrombin-AT III Complex ug/L	4.75 [2.65,12.13]	8.8 [5.3, 12]	14.3 [6.9, 40.7]	0.045	NS	NS	NS
Prothrombin Fragment 1&2 (pMol/L)	275 [164.5,380.5]	311 [163, 492]	301 [258, 709]	NS	NS	NS	NS
CH50 (U Eq/ml)	123.4 [101.75,174.7]	113.4[88.68, 153.43]	114.7 [74.6,158.9]	NS	NS	NS	NS
Complement C5a (ng/ml)	29 [21.5, 36]	36.5[25.5, 48.75]	68 [39.5,122.5]	< 0.001	0.038	0.001	NS
Complement C5 (mg/L)	270 [235.25,290.5]	263[235.25, 279]	276 [220,299.5]	NS	NS	NS	NS
Complement C3 (g/L)	1.5 [1.25,1.77]	1.48[1.33, 1.71]	1.56 [1.16,1.73]	NS	NS	NS	NS
SC5b-9 complex (ng/ml)	1070.46 [836.41,1632.17]	1725.48[1092.62, 2403.3]	2392.66 [1245.68,5145.88]	0.006	NS	0.019	NS
Complement Fragment Bb (ug/ml)	0.2[0.15,0.27]	0.25[0.17, 0.3]	0.29 [0.2,0.43]	NS	NS	NS	NS
Complement C3a ng/ml)	296.88[244.33,345.22]	325.88[248.33, 484.03]	460.23 [282.49,652.1]	NS	NS	NS	NS

*P-values given a Bonferroni adjustment to allow for multiple testing between subgroups