Bacterial infection, antibiotic use and COVID-19: Lessons from the intensive care unit

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Background. Empirical broad-spectrum antibiotics are frequently prescribed to patients with severe COVID-19, motivated by concern about bacterial coinfection. There is no evidence of benefit from such a strategy, while the dangers of inappropriate antibiotics are well described.
Objectives. To investigate the frequency, profile and related outcomes of infections by bacterial pathogens in patients admitted to an intensive care unit (ICU) with severe COVID-19 pneumonia.
Methods. This was a prospective, descriptive study in a dedicated COVID-19 ICU in Cape Town, South Africa, involving all adult patients admitted to the ICU with confirmed COVID-19 pneumonia between 26 March and 31 August 2020. We collected data on patient comorbidities, laboratory results, antibiotic treatment, duration of admission and in-hospital outcome.
Results. We included 363 patients, who collectively had 1 199 blood cultures, 308 tracheal aspirates and 317 urine cultures performed. We found positive cultures for pathogens in 20 patients (5.5%) within the first 48 hours of ICU admission, while 73 additional patients (20.1%) had positive cultures later during their stay. The most frequently isolated pathogens at all sites were *Acinetobacter baumannii* (n=54), *Klebsiella* species (n=13) and coagulase-negative staphylococci (n=9). Length of ICU stay (p<0.001) and intubation (p<0.001) were associated with positive cultures on multivariate analysis. Disease severity (p=0.5), early antibiotic use (p=0.5), diabetes mellitus (p=0.1) and HIV (p=0.9) were not associated with positive cultures. Positive cultures, particularly for tracheal aspirates (p<0.05), were associated with longer ICU length of stay and mortality. Early empirical antibiotic use was not associated with mortality (odds ratio 2.5; 95% confidence interval 0.95 - 6.81).
Conclusions. Bacterial coinfection was uncommon in patients at the time of admission to the ICU with severe COVID-19. Avoiding early empirical antibiotic therapy is therefore reasonable. Strategies to avoid coinfection and outbreaks in hospital, such as infection prevention and control, as well as the strict use of personal protective equipment, are important to improve outcomes.

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SARS-CoV-2 is a novel virus that has spread around the world. Its clinical presentation ranges from asymptomatic or mild viral infection to severe, life-threatening hypoxic pneumonia.[1-4] As it is a novel condition, pharmacological treatment regimens for COVID-19 are varied and largely experimental. At the time of writing (December 2020), benefit had only been demonstrated with corticosteroids.[5] In general, antibiotics are the cornerstone of the management of community-acquired pneumonia, and their empirical use continues to be recommended in many guidelines and institutional protocols specific to COVID-19 pneumonia owing to challenges in conclusively ruling out bacterial coinfection.[6-8]

Bacterial superinfection is an important cause of disease severity and mortality in influenza. *Streptococcus pneumoniae* and *Staphylococcus aureus* are frequently implicated.[9] The concern that similar mechanisms may be at work in severe SARS-CoV-2 infection initially motivated the administration of empirical antibiotic therapy in patients admitted with COVID-19 pneumonia. A recent meta-analysis has shown low rates of bacterial coinfection and superinfection in hospitalised patients with COVID-19, ranging from 3% to 14%. These low rates have also been found in previous coronavirus epidemics,[10-12] but may not apply in settings with a higher burden of infectious disease including HIV and tuberculosis.[13-15]

Despite low rates of bacterial infection in patients with COVID-19, antibiotic use remains high, with broad-spectrum agents predominantly being used, conferring dubious benefit.[16] The collateral damage associated with inappropriate antibiotic use is well described and includes increased morbidity, mortality and cost; the occurrence of side-effects, adverse events and toxicity; and contribution to

antibiotic selective pressure driving the global threat of antibiotic resistance.[17-20] More judicious use of antibiotics with consideration for early discontinuation, in keeping with antibiotic stewardship principles, may therefore be appropriate to preserve these agents.

Objectives

To describe the frequency of bacterial coinfection and superinfection and pathogen distribution in adult patients admitted to an intensive care unit (ICU) with COVID-19 pneumonia. We assessed the impact on outcomes of bacterial coinfection and superinfection, and the role of empirical antibiotic use on the emergence of resistance as the pandemic evolved.

Methods

Study design

We performed a prospective descriptive study involving all adult patients with confirmed COVID-19 admitted to the dedicated COVID-19 ICU at Tygerberg Hospital, Cape Town, South Africa, starting from the first case managed at our institution on 26 March 2020 until the study end date on 31 August 2020, corresponding to our first wave.

Data collection

Data were extracted from medical records and entered into a Research Electronic Data Capture (REDCap) database.[21] We extracted information on patient comorbidities, laboratory results, treatment, duration of admission and outcomes from this database for analysis.

General patient management

In our ICU, patient management evolved in keeping with emerging evidence. Initially all patients received empirical broad-spectrum antibiotics (amoxicillin-clavulanate and azithromycin) until viral pneumonia was confirmed, a practice that ceased later in the pandemic. Meropenem was prescribed empirically for hospital-acquired infections, defined as new infections occurring at least 48 hours after admission. Per institutional protocol, all patients had blood cultures and tracheal aspirates performed on ICU admission with follow-up cultures done only when clinically indicated. Our ICU chose a strategy of initial high-flow nasal prong oxygen as our preferred mode to support oxygenation, with intubation and ventilation reserved for patients in whom this method failed.[22] Patients were initially managed with high-dose hydrocortisone or methylprednisolone, but following evidence from the RECOVERY trial,[5] lower doses of steroids (dexamethasone 8 mg intravenously) were used. There was very limited use of specific antiviral therapies (e.g. chloroquine and remdesivir).

Virological diagnosis

All cases of COVID-19 were confirmed by reverse transcriptase polymerase chain reaction for SARS-CoV-2, performed on respiratory isolates including nasal swabs, sputum and/or tracheal aspirates.

Identification of bacterial pathogens

All cultures were submitted to the on-site National Health Laboratory Service microbiology laboratory and processed using standard procedures entailing inoculation of basic agar plates, followed by overnight incubation and follow-up of relevant isolates for urine and respiratory samples. For blood cultures, the automated BacT/Alert blood culture incubation system and BacT/Alert FA or FN Plus bottles (Biomérieux, France) are used. Blood cultures are incubated in the instrument as soon as possible after arrival in the laboratory. After flagging positive, a Gram stain is performed from the blood culture broth, clinicians are informed of the microscopy result, and appropriate media are inoculated for overnight incubation. Identification and antibiotic susceptibility testing of cultured isolates involves use of the automated VITEK 2 system (Biomérieux, France) and/or disc diffusion testing, which are interpreted using annually published Clinical Laboratory Standards Institute breakpoints. Manual methods of identification are used for identification in specific circumstances.

Classification of organisms

'Contaminants' are bacteria that are not actually present at the sample site, but are accidentally inoculated in the culture during collection or processing and give rise to a false-positive culture. 'Colonisers' are bacteria that grow on a body surface exposed to the environment without causing any infection. Differentiating contaminants and colonisers from true pathogens is challenging. To address this, we predefined known said organisms (e.g. coagulase-negative staphylococci (CoNS) and *Bacillus cereus*) as contaminants or colonisers if they were only cultured once, and pathogens if they were cultured more than once, in the same patient. Positive culture results were deduplicated based on the site of sample collection, with a positive result showing the same pathogen with the same susceptibility profile within a 14-day period considered a single episode.

Standardised definitions were used to classify antibiotic resistance.[23] Multidrug resistance was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive drug resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories. Pan-drug resistance (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories.

Definitions

'Pandemic time' was defined as the number of days from 26 March 2020 (admission of the first patient with COVID-19 to the ICU) to the day of the event.

In this article, 'early culture' refers to a culture performed within the first 48 hours of ICU admission. When culturing a pathogen, it usually indicates bacterial 'coinfection', defined as an infection occurring simultaneously with the viral infection and present at the time of presentation to hospital.

'Late culture' refers to a culture performed after 48 hours of admission to the ICU. When culturing a pathogen, it usually indicates bacterial 'superinfection', defined as a secondary infection superimposed on the initial viral infection and usually developing in hospital.

The ratio of arterial oxygen partial pressure to the fraction of inspired oxygen (P/F ratio) was used as a marker of disease severity.

Comorbidities were captured as recorded in the medical records by the primary clinician.

Outcome measures

The primary outcome measures were positive blood, urine and/or tracheal aspirate cultures. Secondary outcome measures included time to positive culture, length of stay, presence of antibiotic resistance and in-hospital mortality.

Statistical analysis

Statistical analysis was performed using R 3.6.2 (R Core Team, USA). Statistical significance was set at $p<0.05$ and a 95% confidence interval (CI) was used. Pearson's χ^2 test was used to identify associations between categorical variables and the outcomes of

interest. When comparing the means of continuous data, the *t*-test was used to assess normally distributed variables while the non-parametric Wilcoxon rank-sum test was used to assess variables that did not follow a normal distribution pattern. To assess for independent factors associated with positive culture and mortality, multivariable logistic regression was used. Variables in the final model were selected based on the researchers' subject knowledge, accounting for the number of parameters the model could support. To assess whether pandemic time was associated with positive culture or increasing levels of antibiotic resistance, we assessed various factors in a multivariable model adjusting for the effect of length of time in the ICU. Multivariate analyses are reported as odds ratios (ORs) with their corresponding 95% CIs.

Ethical considerations

The study was approved by the Health Research Ethics Committee of Stellenbosch University (ref. no. N20/04/002_COVID-19).

Results

We included 363 patients. Outcome data were available for all patients. The mean age (standard deviation (SD)) of the patients was 53.4 (10.5) years. Comorbidities, admission oxygenation status and admission laboratory results are shown in Table 1.

Culture results

We extracted results for 1 199 blood cultures, 308 tracheal aspirates and 317 urine cultures. One hundred and thirty-three blood cultures (11.1%) in 65 patients, 54 tracheal aspirates (17.5%) in 42 patients and 19 urine cultures (6.0%) in 19 patients cultured pathogens.

In 20 patients (5.5%) pathogens were cultured on early cultures, while a further 73 patients (20.1%) had late cultures that were positive. The distribution by site is shown in Table S1 in the Appendix (supplementary file available at http://samj.org.za/public/sup/15590.pdf). Late blood cultures were 15.4 times (95% CI 9.0 - 26.5) more likely to be positive than early blood cultures (p<0.0001), while late

Table 1. Baseline characteristics of the study population

Characteristic	
Age (years), mean (SD)	53.4 (10.5)
Comorbidities, *n* (%)	
High body mass index	249 (68.6)
Hypertension	220 (60.6)
Diabetes mellitus	182 (50.1)
HIV-positive	53 (14.6)
CD4 count on admission (cells/μL), median (IQR)	295 (166 - 462)
Viral load (copies/mL), median (IQR)	<40 (<40)
Dyslipidaemia	40 (11.0)
Asthma	18 (5.0)
Ischaemic heart disease	10 (2.8)
Current tuberculosis	2 (0.6)
Previous tuberculosis	24 (6.6)
Chronic kidney disease	14 (3.9)
Admission oxygenation status	
PaO_2 (kPa), median (IQR)	7.2 (6.0 - 8.9)
P/F ratio, median (IQR)	77.8 (54.6 - 115.7)
Admission laboratory results (reference range)	
Urea (mmol/L) median (IQR) (2.1 - 7.1)	6.4 (4.5 - 9.0)
Creatinine (μmol/L), median (IQR) (64 - 104)	77 (63 - 107)
White cell count (× 10^9/L), mean (SD) (3.92 - 10.40)	12.0 (5.1)
Haemoglobin (g/dL), mean (SD) (13.0 - 17.0)	13.1 (1.8)
Platelet count (× 10^9/L), mean (SD) (171 - 388)	307.0 (117.2)
Absolute neutrophil count (× 10^9/L), mean (SD) (1.60 - 6.98)	10.0 (4.5)
Absolute lymphocyte count (× 10^9/L), mean (SD) (1.40 - 4.20)	1.1 (0.6)
Neutrophil to lymphocyte ratio, mean (SD)	11.8 (8.3)
Absolute eosinophil count (× 10^9/L), median (IQR) (0.00 - 0.95)	0.02 (0.01 - 0.04)
C-reactive protein (mg/L), mean (SD) (<10)	207 (119)
Procalcitonin (μg/L), median (IQR) (<0.1)	0.45 (0.20 - 1.09)
International normalised ratio, median (IQR)	1.13 (1.05 - 1.2175)
D-dimer (mg/L), median (IQR) (0.00 - 0.25)	1.08 (0.46 - 5.7)
HbA1c (%), median (IQR)	6.7 (6.2 - 9.5)
Troponin T (ng/L), median (IQR) (≤14)	13 (8 - 32)
ProB-type natriuretic peptide (ng/L), median (IQR) (<300)	350 (96 - 1 223)
Ferritin (μg/L), median (IQR) (30 - 400)	1 094 (689 - 1 744)
Alanine transaminase (U/L), median (IQR) (10 - 40)	31 (21 - 50)

SD = standard deviation; IQR = interquartile range; PaO_2 = arterial oxygen partial pressure; P/F ratio = ratio of PaO_2 to the fraction of inspired oxygen; HbA1c = glycated haemoglobin.

tracheal aspirates were 6.0 times (95% CI 2.6 - 13.6) more likely to be positive than early tracheal aspirates ($p<0.0001$) and late urine cultures were 3.0 times (95% CI 1.1 - 8.1) more likely to be positive than early urine cultures ($p=0.03$).

We identified over 20 different pathogens (Table 2 and Table S2 and Figs S1 - S3 in the Appendix (http://samj.org.za/public/sup/15590.pdf)), the most common being *Acinetobacter baumannii*, *Enterococcus faecalis*, *Klebsiella* species and CoNS. The organisms identified in early cultures were different from those found in late cultures. CoNS was the most frequent organism in the first 2 days and *A. baumannii* thereafter.

Risk factors for positive culture

After adjusting for covariates, length of ICU stay, intubation and later pandemic time were associated with positive culture for a pathogen, while the number of concurrently admitted patients showed a slight protective effect. Disease severity on admission, age, comorbidities and early antibiotic use were not associated with coinfection or superinfection (Table 3).

Association of culture results with mortality and length of stay

Positive blood culture for pathogens showed a trend towards increased odds of mortality (OR 7.71; 95% CI 0.963 - 100.172; $p=0.08$) and was associated with longer ICU stay (mean (SD) 15.8 (3.2) days compared with 9.5 (0.7) days for patients without a positive culture; $p=0.0002$). The most common organism, *A. baumannii*, was associated with a 6.6 times (95% CI 1.5 - 29.1) increased odds of mortality ($p=0.004$).

A positive pathogen culture on urine was not associated with mortality ($p=1$), but was associated with longer ICU stay (mean (SD) 17.9 (6.4) days v. 10.3 (0.8) days; $p=0.02$) when compared with patients with a negative urine culture.

A positive pathogen culture on tracheal aspirate was associated with increased odds of mortality (OR 34.1; 95% CI 2.013 - 818.06; $p<0.05$) and with a longer ICU stay (mean (SD) 16.3 (4.4) days, compared with 9.9 (0.8) days for patients with no growth; $p=0.006$).

Other risk factors associated with mortality were P/F ratio, intubation and age (Table 3).

People living with HIV

HIV infection was not associated with higher odds of positive blood culture ($p=0.6$), tracheal aspirate ($p=0.8$) or urine culture ($p=1$) for pathogens.

The most common pathogen identified in this group of patients was *A. baumannii* ($n=9$). There were single occurrences of CoNS, *K. pneumoniae*, *E. faecalis*, *Candida glabrata*, *Enterobacter cloacae*, *K. oxytoca*, *Escherichia coli*, *Pseudomonas fluorescens* and *Bacteroides caccae*.

Antibiotic use and resistance

A high rate of empirical antibiotic use was prescribed early in the pandemic as per unit protocol (see 'Methods'). Amoxicillin-clavulanate, azithromycin and meropenem were predominantly used. The use of these antibiotics decreased in the latter half of the pandemic, following a unit policy change as shown in Fig. 1.

The presence of antibiotic resistance was noted predominantly in the latter half of the pandemic, as shown in Fig. 2. We also observed

Table 2. Frequency of cultured pathogens (*n*) by culture site and timing of culture during intensive care unit admission

	Blood culture		Tracheal aspirate		Urine culture	
Organism	**Early**	**Late**	**Early**	**Late**	**Early**	**Late**
Gram-negative organisms						
Acinetobacter baumannii	0	24	1	27	0	2
Klebsiella species	0	4	1	6	0	2
Pseudomonas aeruginosa	0	3	0	2	0	0
Escherichia coli	0	0	0	0	3	2
Enterobacter cloacae	1	3	0	1	0	0
Stenotrophomonas maltophilia	0	3	1	0	0	0
Serratia marcescens	0	2	0	1	0	0
Proteus mirabilis	0	1	0	0	0	1
Haemophilus influenzae	0	0	0	1	0	0
Pseudomonas fluorescens	0	1	0	0	0	0
Chryseobacterium indologenes	0	1	0	0	0	0
Morganella morganii	0	1	0	0	0	0
Gram-positive organisms						
Coagulase negative staphylococci	5	4	0	0	0	0
Enterococcus faecalis	1	5	0	0	2	4
E. faecium	0	3	0	0	0	3
Bacillus species	0	3	0	0	0	0
Staphylococcus epidermidis	0	1	0	0	0	0
Anaerobes						
Mycobacterium tuberculosis	0	0	1	1	0	0
Clostridium perfringens	0	1	0	0	0	0
Bacteroides caccae	0	0	1	0	0	0
Yeasts						
Candida species	2	3	0	0	0	0

Table 3. Risk factors for adverse outcomes in patients with COVID-19 admitted to the ICU, adjusted for covariates

	Unadjusted OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Risk factors for positive culture						
Length of ICU stay	1.07	1.042 - 1.109	<0.001	1.09	1.048 - 1.134	<0.001
P/F ratio	1.00	0.997 - 1.003	0.905	1.00	0.99 - 1.002	0.547
Diabetes mellitus	0.81	0.504 - 1.299	0.383	0.65	0.365 - 1.16	0.1483
Early antibiotic use	0.87	0.521 - 1.457	0.578	1.29	0.659 - 2.59	0.461
Concurrently admitted patients	0.98	0.951 - 1.007	0.131	0.94	0.901 - 0.981	<0.01
Intubated	7.03	4.02 - 12.899	<0.001	8.5	4.567 - 16.766	<0.001
HIV-positive	0.93	0.46 - 1.794	0.844	0.95	0.412 - 2.084	0.898
Age	1.03	1.002 - 1.05	<0.05	1.02	0.99 - 1.042	0.119
Pandemic time	1.01	1.005 - 1.02	<0.01	1.02	1.006 - 1.026	<0.01
Risk factors for mortality						
Resistance						
MDR	2.31	0.548 - 15.708	0.30	2.05	0.095 - 36.983	0.631
XDR	11.24	2.262 - 203.855	<0.05	39.48	0.276 - 59 396.547	0.348
PDR	2.83	1.272 - 7.206	<0.05	0.16	0.008 - 3.666	0.241
Length of ICU stay	0.88	0.839 - 0.91	<0.001	0.74	0.668 - 0.797	<0.001
P/F ratio	1.00	0.991 - 0.998	<0.01	0.99	0.984 - 0.998	<0.05
Diabetes mellitus	1.31	0.855 - 2.027	0.213	1.17	0.538 - 2.539	0.691
Early antibiotic use	2.06	1.293 - 3.286	<0.01	2.48	0.948 - 6.814	0.069
Concurrently admitted patients	1.05	1.017 - 1.074	<0.01	1.03	0.966 - 1.105	0.355
Intubated	22.71	12.371 - 44.875	< 0.001	191.3	48.157 - 1 107.636	<0.001
Positive blood culture	3.66	1.867 - 7.873	<0.001	7.71	0.963 - 100.172	0.082
Positive tracheal aspirate	4.66	1.945 - 13.821	<0.01	34.1	2.013 - 818.06	<0.05
HIV-positive	1.47	0.791 - 2.872	0.236	3.08	0.958 - 10.452	0.064
Age	1.03	1.013 - 1.056	<0.01	1.05	1.011 - 1.094	<0.05
Pandemic time	1.0	0.997 - 1.011	0.239	0.99	0.978 - 1.011	0.533

OR = odds ratio; CI = confidence interval; ICU = intensive care unit; P/F ratio = ratio of arterial oxygen partial pressure to fraction inspired concentration of oxygen; MDR = multidrug resistance; XDR = extensive drug resistance; PDR = pan-drug resistance.

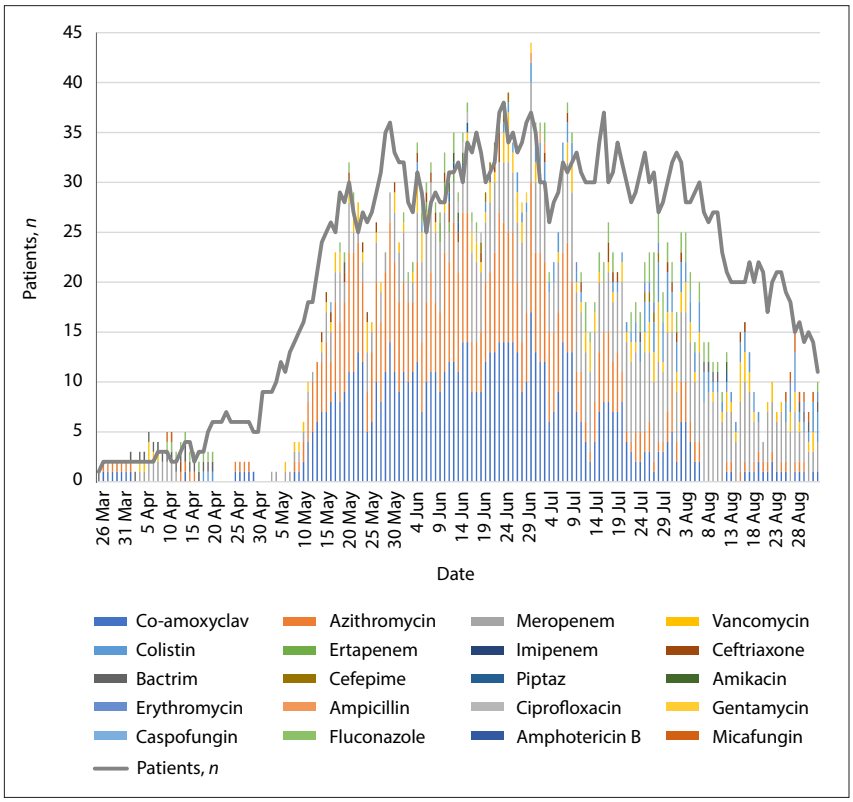

Fig. 1. Number of patients receiving each antimicrobial agent, by day, 26 March - 31 August 2020.

an outbreak of XDR and PDR *A. baumannii* in the same period. Because of this and the short time frame of the study, no further statistical analysis on the evolution of antibiotic resistance was performed.

Early empirical antibiotics within the first 48 hours of admission were prescribed to 258 of the 363 adult patients included. We found no benefit from early antibiotic use, which was associated with a 2.06 times (95% CI 1.293 - 3.286) increased odds of mortality (p<0.01) in unadjusted analysis. The strength of this association was lost after adjusting for covariates (p=0.069), as shown in Table 3.

Discussion

We observed low rates (5.5%) of early bacterial coinfection in patients admitted with severe COVID-19, despite routine cultures being performed on admission to the ICU. There were also low rates of bacterial coinfection overall, with few organisms traditionally associated with community-acquired pneumonia cultured.[6,9] However, when pathogens were identified on culture, they were associated with poor outcomes. We failed to demonstrate an association between

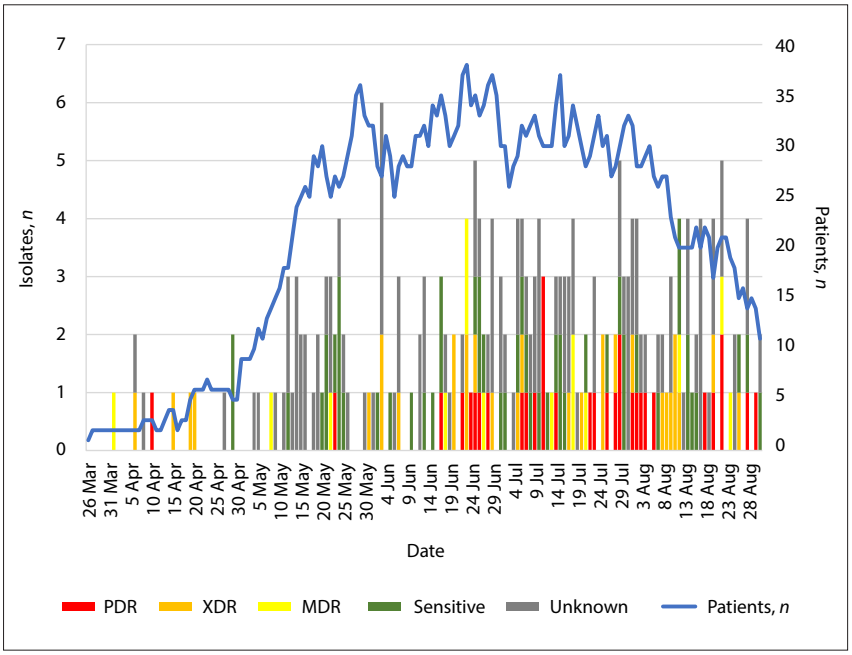

Fig. 2. Resistance profiles of isolates over the course of the pandemic, 26 March - 31 August 2020. (PDR = pan-drug resistance; XDR = extensive drug resistance; MDR = multidrug resistance.)

HIV and bacterial coinfection in COVID-19. Early empirical use of antibiotics in patients with confirmed COVID-19 pneumonia was not associated with improved outcomes (mortality or length of stay) and may have contributed to the observed emergence of resistant organisms in the second half of the study period, although an outbreak of *A. baumannii* – endemic at our institution, and which occurred during the pandemic in spite of strict personal protective equipment (PPE) policies and availability – also played a role. The outbreak may have skewed the temporal relationship, distribution of organisms and resistance patterns found.[24] *A. baumannii* was also the most frequently identified organism, cultured as early as patient day 3 and peaking at days 5 - 7, suggesting early colonisation on or before arrival in the ICU.

The finding of low numbers of early positive cultures for pathogens suggests that the presentation of severe COVID-19 in this population is probably due to the effects of the SARS-CoV-2 virus itself, rather than any bacterial coinfection, as may occur with influenza.[9] Unit policy initially dictated empirical therapy with amoxicillin-clavulanate and azithromycin for all severe presumed COVID-19 pneumonia, and a lack of microbiological evidence of early coinfection in our cohort provides a biological explanation for the failure of this strategy to improve outcomes. Instead, we found that early antibiotic therapy was paradoxically associated with increased mortality. However, many confounding factors may have influenced this observation, including patients being more severely ill or being treated earlier in the pandemic when we had less experience and fewer resources were available.

Our study contributes to a growing body of literature suggesting that bacterial coinfection and superinfection are uncommon in COVID-19 and that early use of empirical antibiotic therapy in these patients, in the absence of a specific bacterial infection, is unnecessary and potentially harmful.[10-12,16,17] Some authors have speculated about an increased rate of fungal coinfection in our setting, and possible excess mortality associated with it, but this has not been borne out in our study.[14]

Positive blood and respiratory cultures (but not urine cultures) demonstrated associations with mortality and length of stay. Strikingly, positive tracheal aspirates were more strongly associated with mortality ($p<0.05$) than positive blood cultures ($p=0.082$), although the small proportion of patients with positive cultures may be a reason for failing to reach statistical significance with the latter. Strategies to avoid bacterial coinfection are therefore vitally important in patients with COVID-19. Intubation was independently associated with infection, and this may in part explain the success reported by some institutions using oxygenation strategies that avoid intubation, such as high-flow nasal prong oxygen.[22]

The lack of association between HIV and bacterial coinfection or superinfection during COVID-19 in our population is also noteworthy ($p=0.9$). However, caution must be exercised when interpreting this finding owing to the small size of the HIV-positive subpopulation, and inherent bias when allocating scarce ICU resources to patients with better virological suppression and higher CD4 counts (i.e. more immunocompetent individuals), as well as other possible unassessed confounders.[25] Similarly, we did not find associations between diabetes and bacterial co-infection or superinfection, and only ICU length of stay, intubation and pandemic time showed significant associations with positive culture results for pathogens, while severity of illness did not.

Despite the compulsory use of PPE, there was a clear emergence of drug-resistant organisms in the latter half of the pandemic, predominantly *A. baumannii*, which has also been reported at other institutions experiencing a surge in COVID-19 admissions to the ICU.[24] There are many likely factors contributing to this observation, including abnormally high patient loads and patient-to-staff ratios, high turnover of beds and staff, increased antibiotic use and PPE fatigue. In response to the COVID-19 pandemic, a significant effort was made to improve PPE for staff. Despite this, hospital-acquired infection remained the biggest contributor to the bacterial pathogens isolated during the study period. We postulate that the increased use of PPE, perceived to protect staff rather than patients, paradoxically increased the likelihood of contamination by serving as a vector for transfer of organisms, and standard infection control measures (e.g. handwashing, glove changing and meticulous cleaning of equipment) should not be forgotten. Multivariate analysis was not able to confirm the association between antibiotic resistance and mortality seen on unadjusted analysis, suggesting a complex interaction of confounding factors.

As evidence to the contrary accumulates, future guidelines for the inpatient management of COVID-19 need to reconsider the blanket recommendation to prescribe empirical antibiotics to all critically ill COVID-19 patients. A subgroup of patients with coinfection may exist and require antibiotics. However, traditional inflammatory markers may be raised by COVID-19 itself and may not be helpful in identifying these patients. In particular, while a low procalcitonin (PCT) level provides confidence to omit antibiotics, high PCT does not necessarily imply the presence of bacterial infection and need for

antibiotics.[1,3,4] Further research is needed to identify specific cut-off thresholds in COVID-19 patients. Other studies are needed to confirm our findings, in particular the lack of association with HIV and bacterial coinfection and superinfection in COVID-19. Standard infection control measures should not be seen to be replaced by PPE where COVID-19 patients are cohorted, and clinicians should be aware of the potential for emergence of antibiotic-resistant organisms, especially during a pandemic.

Study limitations

While all patients have cultures performed on admission to the ICU according to institutional protocol, repeat cultures are performed only when clinically indicated and not routinely. Assessing whether organisms are contaminants, colonisers or pathogens is also imprecise. Indeed, organisms such as CoNS and *B. cereus* are frequently contaminants but may also cause infection, and this distinction can be difficult in critically ill patients, even at the bedside. The number of infections analysed in this study could therefore be either over- or under-inflated. For example, despite our strategy for removing potential contaminants, CoNS remained the most frequently identified organism during the first 2 days of ICU admission. No molecular testing was done to confirm the *A. baumannii* outbreak, as this was detected retrospectively. As in any study in an ICU, our findings are subject to the heterogeneity of the patients and many known and unknown confounders. Associations do not necessarily imply causality or prediction.

Conclusions

Bacterial co-infection is rare at the time of ICU admission with COVID-19, supporting a strategy of withholding early empirical antibiotic therapy, which may help to limit antimicrobial resistance. Late infection after 2 days of admission was more common than early infection and was associated with intubation, length of stay and mortality. Infection prevention and control bundles, strict use of PPE to protect both patients and staff from nosocomial infections and outbreaks, and oxygenation strategies that avoid intubation may therefore prove to be important aspects of COVID-19 care.

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1. Parker A, Koegelenberg CF, Moolla M, et al. High HIV prevalence in an early cohort of hospital admissions with COVID-19 in Cape Town, South Africa. S Afr Med J 2020;110(10):982-987. https://doi.org/10.7196/SAMJ.2020.v110i10.15067
2. Moolla M, Parker A, Parker M, et al. Staff testing for coronavirus disease 2019 via an online pre-registration form. S Afr J Infect Dis 2020;36(1):a232. https://doi.org/10.4102/sajid.v36i1.232
3. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-1720. https://doi.org/10.1056/NEJMoa2002032
4. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ 2020;369:m1985. https://doi.org/10.1136/bmj.m1985
5. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. N Engl J Med 2020;384(8):693-704. https://doi.org/10.1056/NEJMoa2021436
6. Boyles TH, Brink A, Calligaro GL, et al. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis 2017;9(6):1469-1502. https://doi.org/10.21037/jtd.2017.05.31
7. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 2020;46(5):854-887. https://doi.org/10.1007/s00134-020-06022-5
8. Richards G, Mer M, Schleicher G, et al. COVID-19 and the rationale for pharmacotherapy: A South African perspective. Wits J Clin Med 2020;2(S1):11-18. https://doi.org/10.18772/26180197.2020.v2nSIa2
9. Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and bacterial superinfection: Illuminating the immunologic mechanisms of disease. Infect Immun 2015;83(10):3764-3770. https://doi.org/10.1128/IAI.00298-15
10. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. Clin Microbiol Infect 2020 (epub 22 July 2020). https://doi.org/10.1016/j.cmi.2020.07.016
11. Lansbury L, Lim B, Baskaran V, et al. Co-infections in people with COVID-19: A systematic review and meta-analysis. SSRN 2020 (epub 11 June 2020). https://doi.org/10.2139/ssrn.3594598
12. Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med 2020;46(11):2071-2074. https://doi.org/10.1007/s00134-020-06219-8
13. Simbayi L, Zuma K, Zungu N, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. Cape Town: HSRC Press, 2018. https://www.hsrcpress.ac.za/books/south-african-national-hiv-prevalence-incidence-behaviour-and-communication-survey-2017 (accessed 30 November 2020).
14. Ezeokoli OT, Pohl CH. Opportunistic pathogenic fungal co-infections are prevalent in critically ill COVID-19 patients: Are they risk factors for disease severity? S Afr Med J 2020;110(11):1081-1085. https://doi.org/10.7196/SAMJ.2020.v110i11.15248
15. Parker A, Shaw J, Karamchand S, et al. HIV and SARS-CoV-2 co-infection: The diagnostic challenges of dual pandemics. S Afr Med J 2020;110(6):473-475. https://doi.org/10.7196/SAMJ.2020.v110i6.14825
16. Clancy CJ, Nguyen MH. Coronavirus disease 2019, superinfections, and antimicrobial development: What can we expect? Clin Infect Dis 2020;71(10):2736-2743. https://doi.org/10.1093/cid/ciaa524
17. Buetti N, Mazzuchelli T, Lo Priore E, et al. Early administered antibiotics do not impact mortality in critically ill patients with COVID-19. J Infect 2020;81(2):e148-e149. https://doi.org/10.1016/j.jinf.2020.06.004
18. Tamma PD, Avdic E, Li DX, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med 2017;177(9):1308-1315. https://doi.org/10.1001/jamainternmed.2017.1938
19. Paruk F, Richards G, Scribante J, et al. Antibiotic prescription practices and their relationship to outcome in South Africa: Findings of the prevalence of infection in South African intensive care units (PISA) study. S Afr Med J 2012;102(7):613-616.
20. Bamford C, Bonorchis K, Elliott E, et al. Antimicrobial susceptibility patterns of selected bacteraemic isolates from public sector hospitals in South Africa. South Afr J Epidemiol Infect 2009;24(4):28-30. https://doi.org/10.1080/10158782.2011.11441461
21. Allwood BW, Koegelenberg CFN, Irusen E, et al. Clinical evolution, management and outcomes of patients with COVID-19 admitted at Tygerberg Hospital, Cape Town, South Africa: A research protocol. BMJ Open 2020;10:e039455. https://doi.org/10.1136/bmjopen-2020-039455
22. Lalla U, Allwood BW, Louw EH, et al. The utility of high-flow nasal cannula oxygen therapy in the management of respiratory failure secondary to COVID-19 pneumonia. S Afr Med J 2020;110(6):432. https://doi.org/10.7196/SAMJ.2020.v110i6.14882
23. Magiorakos A-P, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268-281. https://doi.org/10.1111/j.1469-0691.2011.03570.x
24. Perez S, Innes GK, Walters MS, et al. Increase in hospital-acquired carbapenem-resistant *Acinetobacter baumannii* infection and colonization in an acute care hospital during a surge in COVID-19 admissions – New Jersey, February - July 2020. MMWR Morb Mortal Wkly Rep 2020;69(48):1827-1831. https://doi.org/10.15585/mmwr.mm6948e1
25. Singh JA, Moodley K. Critical care triaging in the shadow of COVID-19: Ethics considerations. S Afr Med J 2020;110(5):355-359. https://doi.org/10.7196/SAMJ.2020.v110i5.14778

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