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RESEARCH ARTICLE

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Bacteriuria and antibiotic use during the third wave of COVID-19 intensive care in Sweden

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ABSTRACT

Background: Urinary tract infections (UTIs) are prevalent among patients carrying indwelling catheters in the intensive care unit (ICU). This study investigates antibiotic use and bacterial colonisation among ICU patients during the third wave of the COVID-19 pandemic, building on our prior discovery of increased *Enterococcus* colonisation associated with increased cephalosporin use in early COVID-19.

Methods: Longitudinal urine samples from COVID-19 patients ($n = 109$) with transurethral catheterisation were analysed for bacterial prevalence, further identified via MALDI-TOF. Microbiological results were combined with clinical data obtained daily, assessed and compared with COVID-19 waves 1 and 2.

Results: Patients in wave 3 exhibited improved outcomes compared to those in waves 1 and 2, alongside a decrease in antibiotic use. *Staphylococcus* emerged as the primary bacterium and early colonizer of the urinary tract, potentially due to the absence of antibiotic treatment. Our results imply that length of stay (LOS) correlates solely with enteric pathogens and that antibiotic treatment correlates with colonisation by certain uropathogens, whereas the absence of antimicrobial therapy is associated with rapid colonisation of skin flora. Polymicrobial colonisation was common, predominantly involving Gram-positive bacteria.

Conclusion: Our findings underscore the complexity of bacteriuria in ICU patients, advocating for targeted surveillance and tailored antibiotic approaches to mitigate UTI risk. Insights into antibiotic use and bacterial colonisation are vital for optimising stewardship practices, combating antimicrobial resistance, and enhancing ICU patient outcomes.

KEYWORDS
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Introduction

Urinary tract infections (UTIs) are a common and significant complication among patients with indwelling catheters (IDCs) in the intensive care unit (ICU). These infections not only contribute to increased morbidity and mortality but also extend hospital stays and elevate healthcare costs. The management of UTIs in ICU patients is particularly challenging due to the complex interplay of factors such as the patients' critical condition, the presence of invasive devices, and the frequent use of broad-spectrum antibiotics [1,2].

Globally, UTIs are among the most widespread bacterial infections, affecting more than 150 million people annually [3]. In 2019, over 400 million individuals were affected by UTIs worldwide, resulting in nearly 240,000 deaths and contributing to 5.2 million disability-adjusted life years (DALYs) [4]. In the United States alone, UTIs account for approximately 15% of all antibiotic prescriptions [3].

The coronavirus disease (COVID-19) pandemic has further complicated the landscape of ICU-UTI care. Our previous research in the early waves of COVID-19 identified a concerning trend: increased use of cephalosporins was associated with a rise in *Enterococcus* colonisation [5]. The study found that common UTI bacteria, which are usually treatable with antibiotics, often appeared with *Enterococcus* and survived antibiotic treatment when they were together. While this observation was previously uncharted, parallel research has validated similar results [6–8].

Polymicrobial UTIs are of particular importance in the ICU setting. These infections can complicate treatment and lead to more severe clinical outcomes. For instance, bacteria within polymicrobial communities can protect each other from antibiotics through various mechanisms, such as antimicrobial resistance (AMR) or the formation of biofilms. Gram-positive bacteria in urine are commonly dismissed as contaminants [8], but Gram-positive bacteria such as *Enterococcus* have demonstrated the ability to dampen immunological responses, suggesting their potential significance in UTI progression [9,10].

In the ICU setting, where patients often carry IDCs, the risk of developing antibiotic-resistant UTIs is particularly high. The frequent use of broad-spectrum antibiotics in these environments can select for resistant bacteria, making infections more difficult to manage [11]. By studying the prevalence and types of bacteria in ICU patients with UTIs, and how different antibiotic regimens affect these patterns, healthcare providers can develop more targeted and effective treatment strategies. This can help mitigate the risk of antibiotic resistance, ensuring that antibiotics remain effective for treating UTIs and other infections [12].

This study aims to build on our earlier findings by examining the patterns of antibiotic use and bacterial colonisation among ICU patients during the third wave of COVID-19. By comparing these findings with data from the first two waves, we seek to understand the impact of different antibiotic regimens on the evolving dynamics of urinary bacterial colonisation, and its relatedness to infection and patient outcomes. Our research underscores the need for targeted surveillance and customised antibiotic approaches to mitigate UTI risks and enhance patient well-being in ICU settings.

Material and methods

Sample collection and bacterial identification

This study was carried out as a longitudinal prospective cohort study at the Uppsala University Hospital in Uppsala, Sweden, and included all available ICU facilities treating COVID-19 patients between February 2021, and September 2021. Uppsala with its 245,000 inhabitants is considered the fourth largest city in Sweden (Uppsala.se). Overall, 147 catheterised ICU patients were included in the study, 38 were excluded, and 109 remained for analysis (Supplementary Figure 1). Catheterisation happened on the day of arrival in the ICU, or prior to arrival if transferred from other unit (data unavailable).

Samples and data were collected as previously described by our group [5]. Briefly, clinical data were recorded daily, and urine samples were collected longitudinally bi-daily during weekdays, separate from routine monitoring. Microbial growth identified by clinical microbiology (clinical routine samples, CRS) was in our study only registered as a clinical data point, while urine study samples (USS) were collected longitudinally by us in this study separately from clinical routine. Only COVID-19 patients receiving transurethral catheterisation as part of standard clinical practice were included, and urine was collected aseptically from the catheter into sterile vacutainer tubes and transported cold. Samples were processed within 2h and aliquoted from vacutainers into cryovials with 10% dimethyl sulfoxide (DMSO) and stored in −80 °C. Urine was plated onto Brilliance™ UTI Clarity™ agar and isolates of significant colony-forming unit (CFU) count were identified with matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF) and saved in Brain Heart Infusion (BHI, 10% DMSO) broth. Significance levels were considered $>10^3$ CFU/ml and $>10^5$ for *Staphylococcus epidermidis* in accordance with national guidelines for catheterised patients in ICU settings [13–18]. Additional information on UTI criteria can be found in Supplementary Table 1. All cultivation was carried out at 37 °C. The exact techniques deployed in isolation and characterisation have previously been described in detail, and no deviations were made from these protocols. In this study, it was assumed that evaluating UTI symptoms for the cohort may have been challenging. Since clinical symptoms could not be accurately assessed, the samples are categorised as bacteriuria or non-bacteriuria, rather than being classified as UTIs.

Data processing and statistical analysis

All analysis was performed in GraphPad Prism v10. Correlations were investigated with chi-square tests except in continuous parameters where deviations in means were investigated with two-tailed t-tests. Gaussian distribution (normality) was measured using the D'Agostino-Pearson normality test. A significant difference was identified at p-values less than 0.05 with * denoting <0.05, **<0.01, ***<0.001, and ****<0.0001.

Results

Between February 2021 and September 2021, there were 17,176 cases of COVID-19 in Uppsala County, Sweden. Out of these, 1719 individuals were hospitalised, 254 required ICU care, and 147 were included in the study. A total of 38 ICU patients were lost to follow-up, did not receive transurethral catheterisation or did not produce urine, leaving 109 patients for analysis (Supplementary Figure 1).

Included patients had an average age of 61 (standard deviation [SD]: 13.9), a mean simplified acute physiology score 3 (SAPS3) of 53 (SD: 8.7), and an average length of stay (LOS) of 13 days (SD: 9.1) (Figure 1). There were no significant differences in these parameters between wave 3 and waves 1 and 2. Most participants were male (67%), 27% had pre-existing diabetes mellitus, and the cohort mortality rate was 12% (Table 1).

Overall, patients from wave 3 had better prognoses compared to those from waves 1 and 2. In waves 1 and 2, LOS linearly correlated with bacteriuria, but this was not observed in wave 3. Instead, a significantly lower mean SAPS3 was found in patients with bacteriuria (t-test, *) (Figure 1). Not receiving any antibiotic increased the relative risk (RR) of bacteriuria by 3.7 (95% confidence interval (95% CI): 2.2-5.8, ****) (Table 1). Although it initially seemed counterintuitive that a lower SAPS3 would correlate with bacteriuria, further investigation revealed that a lower SAPS3 also correlated with not having received antibiotics, thus offering an explanation for the deviation (Chi squared, *).

Treatment data was available for 91 patients, of whom 77 (85%) received a total of 201 antibiotic prescriptions (each drug counted only once). On average, each patient was prescribed 2.2 different types of antibiotics, with a range from 0 to 10 (SD: 2.0).

Overall antibiotic use decreased in wave 3 compared to waves 1 and 2. Cephalosporins, mainly cefotaxime, remained the most prescribed antibiotic, followed by penicillins (primarily piperacillin-tazobactam, TZP) and carbapenems (mainly meropenem). However, the relative prescription rates of cefotaxime, TZP and meropenem decreased during wave 3 (Figure 2). A similar decrease was observed for trimethoprim-sulfamethoxazole and azithromycin. Conversely, the most notable increases in relative prescription rates were for cloxacillin, ciprofloxacin and vancomycin.

Urine study samples (USS) were collected separately from clinical routine samples (CRS). Unlike USS, we had no control over the timing, location or reasons for CRS collection, making CRS just another retroactively collected data point. In total, 52% of patients had positive bacterial findings in CRS, primarily *Staphylococcus* (41%) and *Escherichia coli* (15%). *Pseudomonas* (10%) and *Enterococcus* (7%) were also common (Figure 3). Overall, 55% of CRS were Gram-positive. Compared to waves 1 and 2, wave 3 had a similar number of *Staphylococcus* cases, but drastically fewer *Enterococcus* and *Stenotrophomonas* cases.

In total, 32% of patients were identified with bacteriuria in USS, with the most common bacteria being *Staphylococcus* (46%), *E. coli* (14%), and *Enterococcus* (12%). Overall, 70% of USS were Gram-positive. Despite the similarities in species and proportion between USS and CRS, there was no correlation between finding a species in CRS and having bacteriuria in USS (Table 1). This indicates that patients with bacteriuria generally did not have other infections, with a few exceptions. Five species from USS were concurrently found in three pulmonary infections and two bloodstream infections (Supplementary Table 1). Only patients with a UTI characterised in CRS correlated with bacteriuria in USS (chi-square, **).

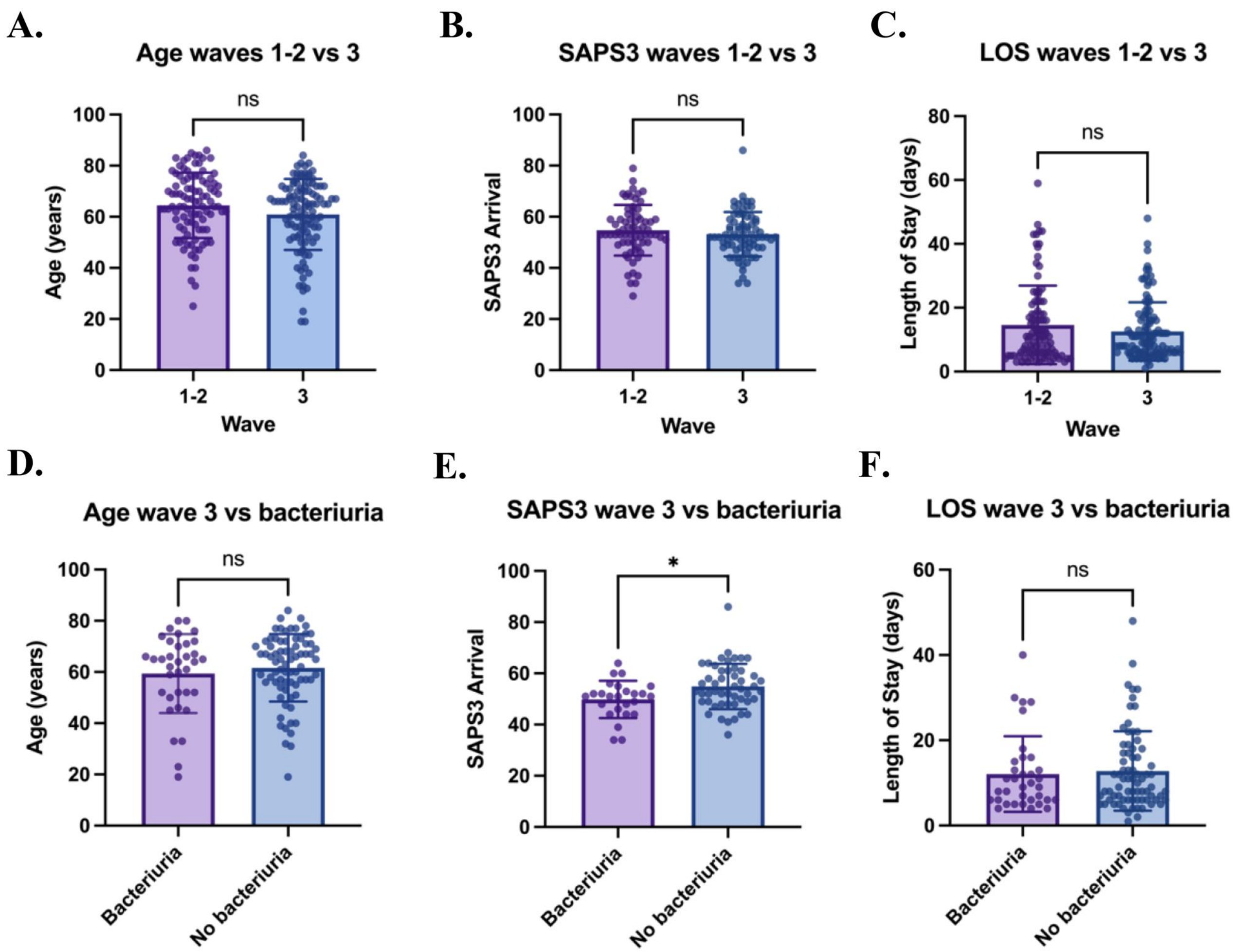

Figure 1. Continuous clinical parameters. Continuous parameters comparing COVID-19 waves 1 and 2 (purple) and 3 (blue) (A–C) and risk of bacteriuria in wave 3 (D–F). All patients were grouped by urine colonisation, yes (purple) and no (blue), compared against three continuous parameters. SAPS3 and LOS represent simplified acute physiology score 3 and length of stay, respectively. The comparison was measured with a two-tailed t-test.

Table 1. Characteristics of enrolled coronavirus disease 2019 (COVID-19) intensive care unit (ICU) patients from wave 3.

Parameter	Bacteriuria	No. of bacteriuria	Total	Relative risk	95% CI	*P*-value	Significance
Sex	35	74	109	1.09	0.83-1.51	0.53	ns
Male	22	51	73	–	–	–	–
Female	13	23	36	–	–	–	–
Diabetes	35	74	109	1.17	0.86-1.49	0.28	ns
Yes	7	22	29	–	–	–	–
No	28	52	80	–	–	–	–
Immunosuppressive	31	60	91	–	–	–	–
Yes	31	60	91	–	–	–	–
No	0	0	0	–	–	–	–
Deceased (30 days)	35	74	109	0.95	0.38-1.95	0.91	ns
Yes	4	9	13	–	–	–	–
No	31	65	96	–	–	–	–
Bacterial finding in clinical routine samples	35	74	109	1.37	0.79-2.41	0.27	ns
Yes	21	36	57	–	–	–	–
No	14	38	52	–	–	–	–
Bacteriuria from clinical routine samples	35	74	109	2.2	1.29-3.59	0.0048	**
Yes	13	10	23	–	–	–	–
No	22	64	86	–	–	–	–
Antibiotic treatment	30	61	91	3.67	2.23-5.78	<0.0001	****
No	12	2	14	–	–	–	–
Yes	18	59	77	–	–	–	–

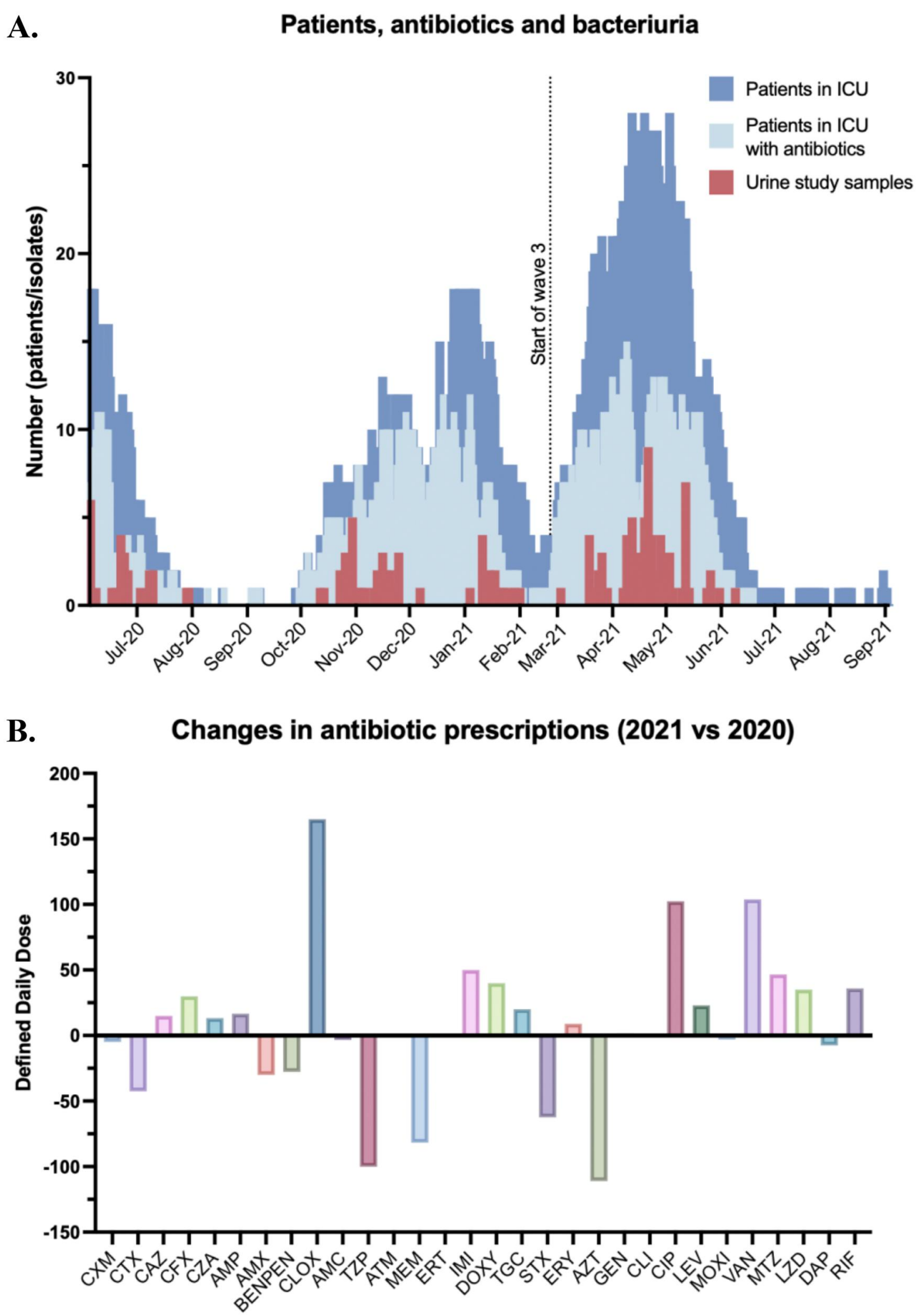

Figure 2. Antibiotic treatment. A. Epidemiological overview of all patients admitted to the Uppsala University Hospital intensive care unit (ICU) (dark blue) according to the Swedish Intensive Care Registry (SIR), the number of ICU patients in our cohort receiving at least one antibiotic (bright blue), and the number of urine study samples identified (red). B. The difference in antibiotic requisition in the Uppsala ICU from 2020 to 2021 presented in defined daily dose. Positive values indicate requisition increase while negative values indicate requisition decrease. CXM: cefuroxime, CTX: cefotaxime, CAZ: ceftazidime, CFX: cefoxitin, CZA: ceftazidime-avibactam, AMP: ampicillin, AMX: amoxicillin, BENPEN: benzyl penicillin, CLOX: cloxacillin, AMC: amoxicillin-clavulanate, TZP: piperacillin-tazobactam, ATM: aztreonam, MEM: meropenem, ERT: ertapenem, IMI: imipenem, DOXY: doxycycline, TGC: tigecycline, STX: trimethoprim/sulfamethoxazole, ERY: erythromycin, AZT: azithromycin, GEN: gentamicin, CLI: clindamycin, CIP: ciprofloxacin, LEV: levofloxacin, MOXI: moxifloxacin, VAN: vancomycin, MTZ: metronidazole, LZD: linezolid, DAP: daptomycin, RIF: rifampicin.

For the three most common bacteria in USS, the first isolate was identified on average on day 4.9 for *Staphylococcus* ($n = 25$, SD: 5.1), day 6.9 for *Escherichia* ($n = 7$, SD: 4.1) and day 12.5 for *Enterococcus* ($n = 6$, SD: 8.7) (Figure 3). The average day of first colonisation for any bacteria without antibiotic administration was 3.4 days ($n = 17$, SD: 1.5) (Supplementary Table 1). This was similar to the average day of first colonisation for cases appearing before the start of antibiotics, which was 3.2 days ($n = 5$, SD: 1.3) as shown in Supplementary Tables 2–4. For first-time colonisation occurring during antibiotic treatment, the average first day was 8.4 days ($n = 7$, SD: 2.8). If colonisation appeared after antibiotic treatment, the average first day was delayed to 20.6 days ($n = 5$, SD: 8.3). In cases where first colonisation occurred before treatment, three events continued during antibiotic exposure, meaning in total, ten patients experienced colonisation while on antibiotics.

Since *Staphylococcus* was the most frequent genus, it confounded the correlation between bacteriuria and LOS. Excluding *Staphylococcus* from the bacteriuria group showed that the correlation between LOS and urine colonisation was true for enteric bacteria (t-test, *). All species appeared several days earlier during wave 3 compared to waves 1 and 2 (not statistically significant) (Figure 3).

Among the 35 patients with bacteriuria, we found 69 isolates. Some isolates were the same species from the same patients but on different days. Considering the same species in the same patient as the same clone, we identified 51 bacterial clones across the 35 patients, resulting in an average of 1.5 bacterial species per bacteriuria-positive patient.

The distribution of monomicrobial/polymicrobial colonisation was as follows: Gram-negative alone (23%, eight patients), Gram-positive alone (37%, 13 patients), polymicrobial with only Gram-negatives (0%, no patients), polymicrobial with only Gram-positives (26%, nine patients) and polymicrobial with both Gram-negatives and Gram-positives (14%, five patients). The Gram-negatives isolated alone were mainly *E. coli*, followed by *Pseudomonas aeruginosa*, *Citrobacter koseri* and *Proteus mirabilis*. Gram-negatives isolated polymicrobially with Gram-positives were mainly *E. coli*, followed by *P. aeruginosa*, *Enterobacter cloacae* and *Klebsiella pneumoniae*. When polymicrobial, Gram-negatives only co-colonize with *Staphylococcus aureus*, *Enterococcus faecalis* and *Staphylococcus capitis*. For Gram-positives, the majority were co-colonisation of different *Staphylococcus* spp., followed by *Staphylococcus* with *Streptococcus*, *Staphylococcus* with *Aerococcus*, *Staphylococcus* with *Enterococcus* and *Staphylococcus* with *Corynebacterium* (Figure 3).

Regarding antibiotic treatment, the highest correlations were found between no antibiotics and colonisation with *S. epidermidis*, followed by cefotaxime treatment and colonisation with *E. coli* (Figure 3). While TZP and cefotaxime were often prescribed to the same patient, *E. coli* never colonised in patients receiving TZP. This trend remained true when looking at relative prevalence (bacteria divided by the total number of prescriptions of that drug, given colonisation). The most common bacteria during penicillin-type treatment were *S. epidermidis*, and the most common bacteria during carbapenem treatment were *P. aeruginosa*

Discussion

In this paper, we explored the correlation between antibiotic use and bacterial colonisation in ICU patients during the third wave of the COVID-19 pandemic, comparing it to our previous investigation where we uncovered a concerning rise in *Enterococcus* colonisation.

There were no significant differences in age, SAPS3 or LOS between different waves of the pandemic. However, patients in wave 3 exhibited a better prognosis and outcome compared to those in waves 1 and 2, with a 6% lower mortality rate [5]. This contrasts with findings from both South Korea and Poland [19,20] while being slightly better than those reported in other parts of Europe [21].

Despite the high prevalence of antibiotic prescriptions, there was a relative decrease in antibiotic use, particularly for cefotaxime, TZP, and meropenem, in wave 3. At the same time, we no longer identified *Enterococcus* as the main coloniser. This shift in antibiotic prescribing practices may reflect changes in clinical management protocols and aligns well with similar studies from the same period [22,23].

A significant association was found between lower SAPS3 (indicating less severe illness), antibiotic treatment and bacteriuria. Patients with lower SAPS3 scores were less likely to have received antibiotics, which, in turn, may have increased their risk of developing bacteriuria. Among the 35 patients identified with bacteriuria, *Staphylococcus* emerged as the most common genus, followed by *Escherichia* and *Enterococcus*. While coagulase-negative *Staphylococcus* often is considered a common skin commensal, it is also frequently

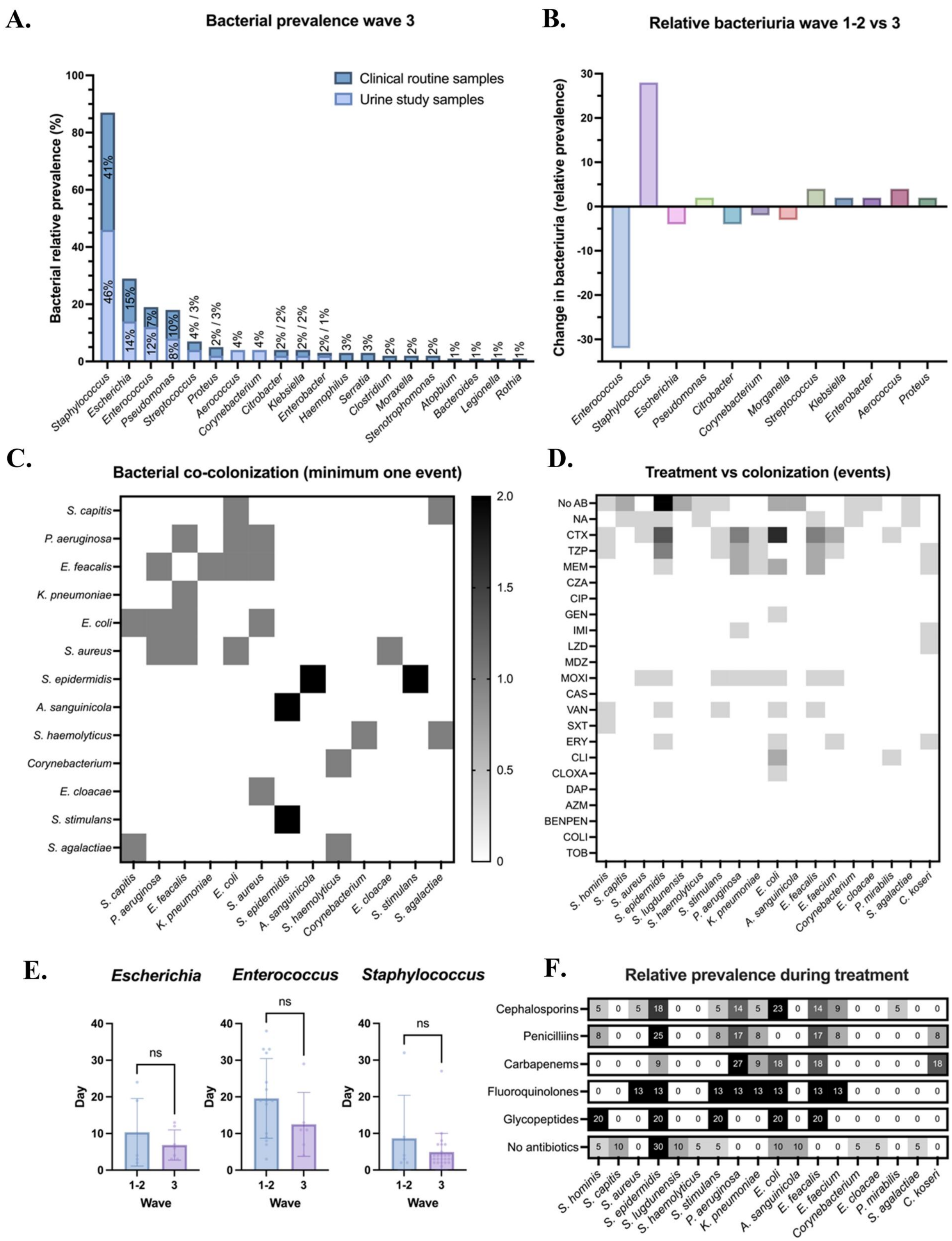

Figure 3. Antibiotic treatment. A. The relative prevalence of identified bacteria in urine study samples (bright blue) and any positive clinical routine sample (dark blue). Each species is counted maximum once per patient. B. Changes in relative bacteriuria comparing wave 1-2 and wave 3. C. Heatmap correlation showing frequency of co-colonisation of different species of bacteria. Species without co-colonisation are not illustrated. D. Heatmap correlation between bacteriuria and antibiotic treatment illustrated in numbers. E. Comparison of the first day of colonisation among the three most common species in waves 1-2 and 3, significance calculated using t-test. F. Correlation heatmap showing the proportion within a species that was exposed to a specific antibiotic. Numbers represent the percentage of isolates exposed to the given antibiotic. The percentage for any given antibiotic can be above 100% as isolates from different species were occasionally co-colonizing during the same treatment.

responsible for nosocomial infections on medical devices [24,25]. It might moreover contribute to easier colonisation and protection from antibiotics and antibodies for secondary bacterial colonisers [26]. In our study, of the isolates identified in USS with a counterpart found in CRS blood, all were coagulase-negative staphylococci. Interestingly, despite similarities in the species composition between urine and other sampling locations, no correlation was generally observed between bacteria in CRS and the presence of bacteriuria in USS, except for CRS urine samples. According to our results, having bacteriuria increased the likelihood of being classified with a UTI (reaching national criteria), while it did not have a measurable impact on infections of other sights. This suggests that patients experiencing bacteriuria had the colonisation confined to this anatomical site.

During COVID-19 wave 3, all bacterial species appeared earlier in the urine compared to the first wave, although this difference was not statistically significant. *Staphylococcus*, the earliest and most frequent coloniser, complicated the association between bacteriuria and LOS. Excluding *Staphylococcus* from the analysis revealed a significant correlation between LOS and colonisation by enteric bacteria. Patients who did not receive antibiotics exhibited higher rates of colonisation with *S. epidermidis*. Combined, these results indicate that patients not receiving antibiotics had a higher risk of developing bacteriuria with skin flora, and that these colonisation events happened early during the ICU stay or catheter insertion, a statement supported by previous literature [27]. In contrast, enteric bacteria required a longer LOS for colonisation, which followed a predictable pattern, as reported for the first waves [5]. Cefotaxime treatment correlated with colonisation by *E. coli*, and *E. coli* colonisation was notably absent in patients receiving TZP. These results indicate that colonisation by more severe uropathogens occurred during antibiotic treatment, while more common skin commensals colonised in the absence of antibiotics, something previously suggested [28]. Colonisation resistance has long been investigated in the intestinal environment [29], but the extent of this occurrence in the bladder remains less explored, although, suggested [30]. Polymicrobial colonisation was observed in nearly half of the cases, similar to other data from Europe [31], with combinations of Gram-positives, or Gram-positives with Gram-negative bacteria, being the most common.

This study has several limitations that should be considered when interpreting the results. This study focused on urine-producing ICU patients, so the findings might not apply to all ICU patients. Differences in clinical management and antibiotic practices across ICUs could influence outcomes. Our bacteriuria criteria ($>10^3$ CFU/ml) might miss certain aggressive infections, and our assay might additionally miss anaerobic bacteria, or bacteria with high CFU counts between collection days. Some patients had catheters before the study, potentially allowing more time for colonisation. Additionally, the lack of UTI diagnostics in Swedish ICUs during the study period limited our ability to predict the impact of bacteriuria on diagnosed UTIs.

The novelty of this research lies in its examination of the impact of antibiotic treatment on bacteriuria and the understanding of bacterial co-colonisation. The study highlights significant changes in antibiotic prescription practices over the pandemic and provides valuable information on the clinical management of COVID-19 ICU patients. These findings emphasise the complexity of bacteriuria in ICU patients, underscoring the need for targeted surveillance and customised antibiotic strategies to reduce the risk of complicated UTIs in this vulnerable population. The correlations between antibiotic treatment and colonisation offer important data for optimising antibiotic stewardship in ICU settings, thereby minimising antimicrobial resistance and improving patient outcomes.

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Author contributions

PK, HW, and JJ: conceptualisation and writing - original draft. PK, LS, CB, MH, and RF: data curation. PK, CB, HW, and JJ: formal analysis. HW, MH, RF, and JJ: funding acquisition. PK, CB, HW, and JJ: investigation. PK, HW, JJ, MH, RF, and ML: methodology. HW, JJ, MH, and RF: project administration. HW and JJ: validation. CB, MH, RF, and ML: writing - review and editing. All authors contributed to the interpretation of results and critical review of the manuscript and had access to the data, except for identifiable clinical data to which access was restricted to those acquiring and analysing it.

Ethics statement

Data found in this research are part of the PronMed study approved by the National Ethical Review Agency [Dnr 2017/043 (with amendments 2020-01623, 2020-02719, 2020-05730, and 2021-01469) and 2022-00526-01)] and listed at ClinicalTrials.gov (NCT03720860). Informed consent was obtained from the patient or next of kin. The Declaration of Helsinki and its subsequent revisions were followed. Adult ICU patients admitted between 25 February 2021 and 3 September 2021 with reverse-transcription polymerase chain reaction (RT-PCR) positive nasopharyngeal swabs were prospectively recruited to the study. Exclusion criteria were pregnancy, current breastfeeding, and age under 18 years. End of follow-up was defined to the end of ICU treatment.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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