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Risk factors and clinical impact of multidrug resistance in healthcare-associated bacteraemic urinary tract infections: a post-hoc analysis of a multicentre prospective cohort in Spain

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SUMMARY

Background: The global burden associated with antimicrobial resistance is of increasing concern.

Aim: To evaluate risk factors associated with multidrug-resistant (MDR) infection and its clinical impact in a cohort of patients with healthcare-associated bacteraemic urinary tract infections (BUTIs).

Methods: This was a prospective, multicentre, post-hoc analysis of patients with healthcare-associated-BUTI (ITUBRAS-2). The primary outcome was MDR profile. Secondary outcomes were clinical response (at 48—72 h and at hospital discharge) and length of hospital stay from onset of BUTI. Logistic regression was used to evaluate variables associated with MDR profile and clinical response. Length of hospital stay was evaluated using multivariate median regression.

Findings: In all, 443 episodes were included, of which 271 (61.17%) were classified as expressing an MDR profile. In univariate analysis, MDR profile was associated with *E. coli* episodes (odds ratio (OR): 3.13; 95% confidence interval (CI): 2.11—4.69, $P < 0.001$) and the extensively drug-resistant (XDR) pattern with *P. aeruginosa* aetiology (7.84; 2.37—25.95; $P = 0.001$). MDR was independently associated with prior use of fluoroquinolones (adjusted OR: 2.43; 95% CI: 1.25—4.69), cephalosporins (2.14; 1.35—3.41), and imipenem or meropenem (2.08; 1.03—4.20) but not with prior ertapenem. In terms of outcomes, MDR profile was not associated with lower frequency of clinical cure, but was associated with longer hospital stay.

Conclusion: MDR profile was independently associated with prior use of fluoroquinolones, cephalosporins, imipenem, and meropenem, but not with prior ertapenem. MDR-BUTI episodes were not associated with worse clinical cure, although they were independently associated with longer duration of hospital stay.

Introduction

Healthcare-associated infections (HAIs) and antimicrobial resistance are currently major global public health threats and multiple reports have warned about the increase in multidrug-resistant (MDR) infections [1]. In a recent study of the global burden of antimicrobial-resistant infections, the number of deaths worldwide in 2019 attributable to antimicrobial resistance was estimated at 4.95 million deaths, making it the third leading cause of death that year after ischaemic heart disease and stroke [2].

Although MDR infections have traditionally been associated with nosocomial infections, there has been a worrying increase in recent years in community-onset MDR infections, typically associated with the healthcare setting [1,3]. HAIs include those acquired during hospital admission, as well as those occurring in ambulatory patients in contact with healthcare settings [4]. In recent decades, HAIs have increased in both number and complexity, and for different reasons. The first includes demographic changes, such as an ageing population, with older, more comorbid patients who require frequent use of medical resources such as daily healthcare services, nursing homes, and long-term care facilities. Second, technological innovations have made it possible to perform more complex therapies on an outpatient basis. Minimally invasive interventions have shorter hospital stays, often resulting in infections being diagnosed after hospital discharge [4]; more specifically, for both the diagnosis and treatment of urinary tract infection (UTI), the number of invasive urologic procedures has increased in recent decades.

UTIs are among the most common infections and one of the most common reasons for hospitalization [4,5]. Indeed, UTIs account for 12—24% of HAIs, with significant differences depending on the country [4]. A further cause for concern is the sharp increase in healthcare-associated UTIs caused by MDR Gram-negative bacteria (GNB) in recent years [1]. In a previous study by our group comparing hospital-acquired and community-onset healthcare-associated bacteraemic UTI (BUTI), we found high rates of MDR in both groups of patients [5]. Whereas multiple reports have evaluated the risk factors and impact of MDR infections in hospital-acquired infections [6], little is known about the epidemiology and potential risk factors associated with MDR infection in healthcare-associated BUTIs, including patients with community-onset HAIs [5,7]. Therefore, we conducted a post-hoc analysis of our cohort. The aim was to evaluate possible risk factors associated with MDR infection in HAI patients with BUTI already admitted to the hospital or who required hospitalization in community-onset cases. We hypothesized that MDR infections were associated with worse clinical outcomes and longer hospital stays. Therefore, as a secondary objective, this study set out to determine whether an MDR profile was independently associated with worse outcomes.

Methods

Study design, setting, and study population

The ITUBRAS-2 project is a prospective, observational, multicentre, cohort study that included consecutive patients

with healthcare-associated BUTIs between August 2017 and April 2019. Twelve tertiary university hospitals belonging to the Spanish Network for Research in Infectious Diseases (REIPI) (www.reipi.org) and CIBERINFEC (www.ciberinfec.es) participated in the project. The overall objective of the ITUBRAS-2 project was to describe the clinical and microbiological characteristics and outcomes of healthcare-associated BUTI, comparing mainly community-onset and hospital-acquired BUTIs. The present study is a post-hoc analysis of the ITUBRAS-2 cohort. The methods of the ITUBRAS-2 study have been detailed previously [5]. Briefly, the study included consecutive adult patients with healthcare-associated BUTI according to Friedman's criteria [8]. BUTI was considered when a patient presented urinary tract symptoms and one or more uropathogens were isolated in blood cultures. BUTI were also defined when patients did not present urinary symptoms but the same uropathogen was isolated in urine and blood cultures and absence of other source of infection. Enterobacterales, *Pseudomonas aeruginosa*, *Enterococcus* spp., *Staphylococcus saprophyticus* and *Streptococcus agalactiae* were defined as potential uropathogens. Polymicrobial episodes were included. Exclusion criteria were patients who did not require hospitalization, non-healthcare-related UTIs, and infections caused by unusual urinary tract pathogens. For this analysis, all patients with healthcare-associated BUTI were eligible, and episodes were classified as MDR or non-MDR based on international consensus definitions [9]. Patients were followed for 30 days.

The study was approved by the Clinical Research Ethics Committee of the Hospital del Mar (registration no. 2016/6957/I) and by the local ethics committees of the participating centres. All patients supplied written informed consent at screening. Patients unable to supply informed consent could be included with the signature of a relative or legal representative. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (Supplementary Table S1).

Variables and definitions

The main objective of the study was to evaluate risk factors associated with healthcare-associated BUTIs with an MDR profile. Secondary outcome variables were early clinical response (assessed at 48–72 h from onset of bacteraemia), clinical response at hospital discharge, and length of hospital stay (days) from the onset of the BUTI until hospital discharge. Persistence of fever (considered as temperature $\geq$38 °C) and/or signs/symptoms of sepsis according to Sepsis-3 international consensus definition 48–72 h after the onset of bacteraemia was considered as non-clinical stability at 48–72 h [10]. Clinical response at hospital discharge was classified as cure (all signs/symptoms of infection were completely resolved at hospital discharge), improvement (the patient improved but with persistence or recurrence of any infection-related signs or symptoms at hospital discharge), and failure (lack of improvement or death). For the analysis, clinical response at hospital discharge was dichotomized into cure/improvement vs failure.

The following data were prospectively recorded: age, gender, site of infection acquisition (nosocomial vs community-onset HAIs), underlying conditions and severity according to the Charlson comorbidity index, prior urologic history, severity at onset of infection according to the Pitt bacteraemia score, antibiotic exposure in the previous 90 days, antimicrobial treatment received (empiric and targeted), clinical response, and length of stay after BUTI [11,12]. Previous use of antibiotic was defined as >48 h of antibiotic treatment in the three months prior to the infection. Antimicrobial treatment was considered appropriate when the isolate was susceptible to one or more of the prescribed antimicrobials. EUCAST breakpoints of the corresponding year of micro-organism isolation (2017, 2018, or 2019) were used.

Microbiology

Bacterial identification was performed by MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) and antimicrobial susceptibility testing was determined by the standard broth microdilution method using EUCAST-2019 interpretive criteria (http://www.eucast.org/clinical_breakpoints/). Isolates were classified according to resistance profile, in accordance with international standard definitions [9]. An MDR strain was defined as non-susceptible to $\geq$1 agent in $\geq$3 antimicrobial categories; extensively drug-resistant (XDR) was defined as non-susceptible to $\geq$1 agent in all but $\leq$2 antimicrobial categories; and pandrug resistant (PDR) was resistance to all antimicrobial agents tested. In case of polymicrobial bacteraemia, the episode was considered MDR if at least one of the isolates had an MDR profile. Therefore, a polymicrobial bacteraemia caused by MDR and non-MDR isolates was considered to be an MDR episode.

Enterobacterales were screened for extended-spectrum β-lactamases (ESBLs) and carbapenemase production using the double-disc synergy method and the colorimetric Carba-NP test (bioMérieux, La Balme-les-Grottes, France), respectively [13,14]. The ceftazidime/imipenem cloxacillin inhibition test was used to detect the presence of horizontally acquired β-lactamases in *P. aeruginosa*, and the imipenem/meropenem–EDTA double-disc synergy method to confirm detection of metallo-β-lactamases [15]. Genes encoding these enzymes were confirmed and characterized by multiplex polymerase chain reaction and further Sanger sequencing [15]. MDR and XDR *P. aeruginosa* strains were further characterized through whole-genome sequencing (Miseq Illumina, San Diego, CA, USA), assessing the involved clone and resistome (horizontally acquired and mutational) as previously described [16].

Statistical analysis

Categorical variables were expressed as numbers of cases and percentages, and were compared with the χ^2-test or Fisher's exact test. Continuous variables were expressed as median and interquartile range (IQR) and compared using the Mann–Whitney *U*-test. Univariate and multivariate logistic regression analysis, using backward stepwise selection, was used to evaluate variables independently associated with an MDR profile and clinical response (both non-clinical stability at 48–72 h and non-clinical cure at hospital discharge). Results were expressed as odds ratios (OR) and 95% confidence interval (CI). Length of hospital stay (days) from the onset of bacteraemia was evaluated by multivariate median regression to deal with the non-normality of dependent variables [17]. The results were expressed as median and 95% CI. Correlations between continuous variables were evaluated with Spearman's rank correlation coefficient. In all models, variables with $P <$

0.20 in univariate comparison and those that were not statistically significant but were considered clinically relevant were included in the multivariate model. In the analysis of MDR profile, Charlson index was considered a clinically relevant variable and was forced in the multivariate analysis. In the multivariate analysis of early clinical response, site of acquisition (nosocomial vs community onset) was considered a clinically relevant variable and forced as it may influence in the time to receive antibiotic treatment, and therefore, in clinical stability. Collinearity was examined by collinearity diagnostics (controlling the variance inflation factor, VIF). Pitt score, septic shock, and ICU admission were highly related; after examination by VIF, only septic shock was included in the multivariate analysis. Finally, a subgroup analysis limited to *Escherichia coli* episodes was performed to evaluate whether risk factors of *E. coli* episodes differ from other pathogens. Variables with >20% missing values were not considered for multivariate analysis. All analyses were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with Stata 15.1. software.

Results

Bacterial isolates and resistance profile

The ITUBRAS-2 cohort includes 443 episodes of healthcare-associated BUTI. Polymicrobial bacteraemia was detected in 22 of these episodes, with a total of 468 bacterial isolates. The aetiologic agents in our study population are shown in Table I. A total of 271 episodes (271/443, 61.17%) were classified as MDR. Of these, 11 isolates had an XDR profile (six Enterobacterales and five *Pseudomonas aeruginosa*) and one *Klebsiella pneumoniae* isolate had a PDR pattern. Four of the five XDR *P. aeruginosa* belonged to the high-risk clone ST175, widely disseminated in Spanish hospitals [18]. None of them produced acquired carbapenemases, but showed the characteristic mutational resistome associated with this high-risk clone, including among them OprD Q142* and AmpR G154R [16]. Six additional *P. aeruginosa* strains showed an MDR (non-XDR) phenotype, including two isolates from clones ST175 and ST253 producing the MBL VIM-1. The XDR/PDR pattern was significantly associated with *P. aeruginosa* (5/41, 2.2%) vs non-*P. aeruginosa* (7/443, 1.6%) ($P = 0.003$). In univariate analysis, MDR profile was associated with *E. coli* episodes (OR: 3.13; 95% CI: 2.11–4.69; $P < 0.001$) and the extensively drug-resistant (XDR) pattern was associated with *P. aeruginosa* aetiology (OR: 7.84; 95% CI: 2.37–25.95; $P = 0.001$). Overall, ESBL- and carbapenemase-production were detected in 25% (117/468) and 3% (14/468, 12 Enterobacterales and 2 MBL-producing P. aeruginosa) of the isolates respectively.

Patient characteristics according to MDR profile are shown in Table II. Compared to patients with non-MDR infection, those in the MDR group more often had underlying diseases, worse Pitt scores at the onset of bacteraemia, and had more often received antibiotic treatment in the previous 90 days. The most commonly used empiric

Table I
Aetiology of 468 isolates in the study population

	Total no. of episodes	Isolation of MDR episodes	Isolation of non-MDR episodes	*P*
Escherichia coli	219	162 (73.97%)	57 (26.03%)	≤0.001
Klebsiella pneumoniae	90	53 (58.89%)	37 (41.11%)	0.618
Proteus mirabilis	20	11 (55.00%)	9 (45.00%)	0.562
Other Enterobacterales	40	14 (35.00%)	26 (65.00%)	≤0.001
Pseudomonas aeruginosa	36	11 (30.56%)	25 (69.44%)	≤0.001
Enterococcus spp.	16	6 (37.50%)	10 (62.50%)	0.048
E. coli + *K. pneumoniae*	3	2[a]	1	–
E. coli + other *E. coli*	3	3	0	
E. coli + other Enterobacterales	2	1[b]	1[c]	–
E. coli + *P. aeruginosa*	1	1[d]	0	–
E. coli + *E. faecalis*	1	0	1	–
K. pneumoniae + other Enterobacterales	5	3[e]	2[f]	–
P. mirabilis + *Morganella morganii*	1	0	1	–
P. aeruginosa + *E. faecalis*	2	0	2	–
E. faecalis + *E. faecium*	1	1	0	–
P. aeruginosa + *E. faecalis* + *K. aerogenes*	1	1 (*K. aerogenes*)	0	–
P. aeruginosa + *E. cloacae* + *K. pneumoniae*	1	1 (*E.cloacae* and *P. aeruginosa*)	0	–
E. coli + *E. coli* + *K. aerogenes*	1	1 (*E. coli* and *E. coli*)	0	
Total	443	271 (61.17%)	172 (38.82%)	

MDR, multidrug resistant (defined as a strain non-susceptible to at least one agent in ≥3 antimicrobial families.
[a] One episode caused by MDR *Escherichia coli* and non-MDR *Klebsiella pneumoniae*; one episode caused by non-MDR *E. coli* and MDR *K. pneumoniae*.
[b] One caused by non-MDR *E. coli* and MDR *Morganella morganii*.
[c] One episode caused by non-MDR *E. coli* and non-MDR *Citrobacter amalonaticus*.
[d] One episode caused by MDR *E. coli* and non-MDR *Pseudomonas aeruginosa*.
[e] One episode caused by MDR *K. pneumoniae* and non-MDR *Serratia marcescens*; one caused by MDR *K. pneumoniae* and non-MDR *C. freundii*; and one by non-MDR *K. pneumoniae* and MDR *K. oxytoca*.
[f] One episode caused by non-MDR *K. pneumoniae* and non-MDR *K. oxytoca*; one episode caused by non-MDR *K. pneumoniae* and non-MDR *S. marcescens*.

Table II
Epidemiological features, predisposing factors and clinical characteristics of patients with bacteraemic urinary tract infections according to the antibiotic resistance profile

Variable	All cases ($N = 443$)	Non-MDR profile ($N = 172$)	MDR profile ($N = 271$)	P
Baseline features				
Gender (female)	155 (35.0%)	60 (34.9%)	95 (35.1%)	1.00
Age (years), median (IQR)	74 (65–82)	73 (64–81)	75 (66–82)	0.068
Charlson index, median (IQR)	3.0 (2.0–5.0)	2.0 (1.0–6.0)	3.0 (2.0–5.0)	0.090
Any underlying disease	402 (90.74%)	148 (86.05%)	254 (93.73%)	0.003
Diabetes mellitus	128 (28.9%)	44 (25.6%)	84 (31.0%)	0.238
Chronic renal failure	135 (30.5%)	50 (29.1%)	85 (31.4%)	0.672
Chronic pulmonary disease	59 (13.3%)	26 (15.1%)	33 (12.2%)	0.392
Cardiovascular disease	135 (30.5%)	54 (31.4%)	81 (29.9%)	0.752
Chronic liver disease	26 (5.9%)	4 (2.3%)	22 (8.1%)	0.012
Vascular/degenerative brain disease	94 (21.2%)	28 (16.4%)	66 (24.4%)	0.044
Malignant disease	182 (41.1%)	70 (40.7%)	112 (41.3%)	0.921
Immunosuppressive therapy	121 (27.4%)	46 (26.9%)	75 (27.7%)	0.913
Previous urological history				
Recurrent UTI (>2 episodes/year)	84 (19.6%)	26 (15.8%)	58 (22.1%)	0.133
Indwelling urinary devices	269 (60.7%)	112 (65.1%)	157 (57.9%)	0.136
Urinary tract abnormalities	209 (47.2%)	74 (43.02%)	135 (49.81%)	0.170
Site of acquisition of the infection				0.065
Nosocomially acquired	220 (49.7%)	95 (55.2%)	125 (46.1%)	
Community-onset healthcare-associated infection	223 (50.3%)	77 (44.8%)	146 (53.9%)	
Friedman criteria				
Previous hospitalization (90 days)	146/223 (65.5%)	48/77 (62.3%)	98/146 (67.1%)	0.554
Urinary devices or urinary procedure[a]	112/223 (50.2%)	44/77 (57.1%)	68/146 (46.6%)	0.911
Resident in long-term care facility	50/223 (22.4%)	13/77 (16.9%)	37/146 (25.3%)	0.178
Previous endovenous (e.v) chemotherapy (30 days)	20/223 (9.0%)	8/77 (10.4%)	12/146 (8.2%)	0.626
Haemodialysis programme	4/223 (1.8%)	1/77 (1.3%)	3/146 (2.1%)	1.00
Specialized ambulatory nursing care (30 days)	10/223 (4.5%)	1/77 (1.3%)	9/146 (6.2%)	0.17
Ward admission				
Medical	361 (81.5%)	131 (76.2%)	230 (84.9%)	0.024
Surgical	63 (14.2%)	31 (18.0%)	32 (11.8%)	0.071
ICU	19 (4.3%)	10 (5.8%)	9 (3.3%)	0.233
Prior antimicrobial therapy				
Any antibiotic (90 days)	315 (71.1%)	103 (59.9%)	212 (78.2%)	<0.001
Fluoroquinolones	72 (16.3%)	16 (9.3%)	56 (20.7%)	<0.001
Non-antipseudomonal penicillins	130 (29.3%)	48 (27.9%)	82 (30.3%)	0.669
Antipseudomonal penicillins	58 (13.1%)	16 (9.3%)	42 (15.5%)	0.062
Cephalosporins	166 (37.5%)	49 (28.5%)	117 (43.2%)	0.002
Carbapenems	87 (19.6%)	25 (14.5%)	62 (22.9%)	0.037
Aminoglycosides	12 (2.7%)	3 (1.7%)	9 (3.3%)	0.383
Clinical presentation				
Pitt score >2	160 (36.2%)	48 (28.1%)	112 (41.3%)	0.006
Septic shock	59 (14.0%)	21 (12.9%)	38 (14.8%)	0.666
ICU admission required	82 (18.7%)	29 (17.3%)	53 (19.6%)	0.615
Irritative urinary symptoms	134 (31.9%)	53 (32.5%)	81 (31.5%)	0.831
Renal pain	47 (11.2%)	18 (11.0%)	29 (11.3%)	1.00
Prostate pain in DRE	8 (1.9%)	5 (3.1%)	3 (1.2%)	0.271
Temperature >38 °C	352 (83.8%)	143 (87.7%)	209 (81.3%)	0.102
Leucocytes ($10^3/\mu L$), median (IQR)	12.0 (8.3–16.8)	12.1 (8.3–16.6)	11.7 (8.3–17.4)	0.906
Treatment				
Empirical antibiotic therapy				
Fluoroquinolones	13 (7.6%)	28 (10.4%)	41 (9.3%)	0.401
Non-antipseudomonal penicillins	85 (19.2%)	41 (23.8%)	44 (16.3%)	0.063
Antipseudomonal penicillins	93 (21.0%)	34 (19.8%)	59 (21.9%)	0.634
Cephalosporins	137 (31.0%)	59 (34.3%)	78 (28.9%)	0.247

(*continued on next page*)

Table II (*continued*)

Variable	All cases ($N = 443$)	Non-MDR profile ($N = 172$)	MDR profile ($N = 271$)	P
Carbapenems	183 (41.4%)	68 (39.5%)	115 (42.6%)	0.553
Group 1[b]	42 (9.5%)	13 (7.6%)	29 (10.7%)	0.319
Group 2[b]	141 (31.9%)	55 (32.0%)	86 (31.9%)	1.000
Aminoglycosides	43 (9.7%)	17 (9.9%)	26 (9.6%)	1.000
Monobactam (aztreonam)	7 (1.6%)	1 (0.6%)	6 (2.2%)	0.256
Inappropriate empirical therapy	84 (18.96%)	17 (9.89%)	67 (24.72%)	<0.001
Length of antibiotic therapy (days), median (IQR)[b]	15.0 (12.0–18.0)	14.0 (11.0–17.0)	15.0 (12.0–18.0)	0.059
Outcomes				
Clinical assessment at 48–72 h				
Afebrile	393 (89.5%)	160 (93.0%)	233 (87.3%)	0.057
Persistence of sepsis, signs/symptoms	49 (11.2%)	13 (7.6%)	36 (13.5%%)	0.063
Clinical cure at hospital discharge	263 (59.4%)	99 (57.6%)	164 (60.5%)	0.553
Length of hospitalization since BUTI episode, median (IQR)	12.0 (8.0–20.0)	10.0 (7.0–15.5)	13.0 (8.0–22.0)	<0.001

MDR, multidrug resistant; IQR, interquartile range; UTI, urinary tract infection; ICU, intensive care unit; DRE, digital rectal examination; BUTI, bacteraemic urinary tract infection.

[a] Indwelling urinary devices and/or an invasive urinary procedure performed within the previous month.

[b] Length of antibiotic therapy (days), including both empirical and targeted antibiotic treatment.

drugs were carbapenems, non-antipseudomonal cephalosporins, and piperacillin–tazobactam, with no differences between groups. Inappropriate empiric antibiotic therapy was more frequent in MDR BUTI than in non-MDR episodes (67 (24.72%) vs 17 (9.89%); $P < 0.001$).

Variables associated with an MDR profile

The univariate and multivariate analysis of variables associated with an MDR profile are shown in Table III. In multivariate analysis, the MDR profile was independently associated with prior use of fluoroquinolones (OR: 2.43; 95% CI: 1.25–4.69), cephalosporins (2.14; 1.35–3.41), and a group 2 carbapenem, i.e. meropenem or imipenem (2.08; 1.03–4.20). However, prior use of a group 1 carbapenem (ertapenem) did not reveal significant associations with an MDR profile. An MDR profile was also independently associated with episodes of *E. coli* bacteraemia (3.34; 2.02–5.53). An analysis limit to patient subgroup with *E. coli* episodes was conducted with no relevant differences in risk factors when comparing with the overall cohort (Supplementary Table S2).

Clinical outcomes

Table IV shows the univariate and multivariate analysis of variables associated with early clinical response, defined as clinical stability at 48–72 h from the onset of bacteraemia. After adjusted analysis, the MDR profile was not associated with worse clinical cure at 48–72 h. Variables associated with non-clinical stability at 48–72 h were *K. pneumoniae* infection (OR: 1.99; 95% CI: 1.10–3.59), receipt of inappropriate empirical therapy (1.94; 1.02–3.71) or the presence of septic shock at the onset of BUTI (3.51; 1.85–6.66). A sensitivity analysis of *E. coli* episodes was conducted to evaluate the non-clinical stability at 48–72 h and no significant differences were observed compared to the overall cohort (Supplementary Table S3). After adjusted analysis, the MDR profile was not associated with less frequent clinical cure at hospital discharge (Supplementary Table S4).

Length of hospital stay

Median hospital stay after BUTI was 12 days (IQR: 8–20); 13 (8–22) days for the MDR group, and 10 (7–15.5) days for non-MDR ($P < 0.001$). The univariate and multivariate analyses of factors related to length of hospital stay are shown in Table V. After multivariate median regression, variables associated with longer hospital stay from the onset of BUTI were the presence of septic shock at the onset of bacteraemia, hospital-acquired infections and MDR profile ($P = 0.002$, $P < 0.001$, and $P = 0.017$, respectively). The MDR profile was an independent factor associated with longer hospital stay compared to non-MDR (median difference in hospital stay, days: 3.08; 95% CI: 0.56–5.61; $P = 0.017$).

Discussion

The present study details the clinical characteristics and outcomes of a cohort of patients with healthcare-associated BUTI who required hospitalization, aiming to evaluate the risk factors associated with MDR infections and whether they were associated with worse clinical outcomes than non-MDR infections. In our cohort, more than 60% of episodes were caused by MDR pathogens. When episodes of MDR and non-MDR BUTI were compared, no statistical differences were observed in age, sex, or severity of underlying conditions by Charlson index. In adjusted analysis, MDR was independently associated with prior use of fluoroquinolones, cephalosporins, and group 2 carbapenems but was not associated with prior use of ertapenem. In terms of outcome, the MDR profile was not associated with less frequent clinical cure but was associated with longer hospital stay. In our study, the MDR profile was independently associated with *E. coli* episodes.

Table III
Univariate and multivariate analysis of parameters associated with MDR profile in healthcare-associated bacteraemic urinary tract infection ($N = 443$)

Variable	Unadjusted OR		Adjusted OR	
	95% CI	*P*-value	95% CI	*P*-value
Baseline features				
Gender (female)	1.01 (0.67–1.51)	0.097	0.69 (0.43–1.11)	0.127
Age	1.01 (1.00–1.03)	0.076	1.01 (0.99–1.03)	0.187
Charlson index	1.04 (0.97–1.12)	0.279	1.06 (0.97–1.15)	0.202
Any underlying diseases	2.57 (1.39–4.84)	0.003		
Diabetes mellitus	1.30 (0.85–2.02)	0.222		
Chronic renal failure	1.11 (0.74–1.70)	0.613		
Chronic pulmonary disease	0.78 (0.45–1.37)	0.379		
Cardiovascular disease	0.93 (0.62–1.41)	0.737		
Chronic liver disease	3.59 (1.33–12.8)	0.009		
Vascular/degenerative brain disease	1.65 (1.02–2.73)	0.042		
Malignant disease	1.03 (0.70–1.52)	0.897		
Immunosuppressive therapy	1.04 (0.68–1.61)	0.863		
Recurrent UTI (>2 episodes/year)	1.51 (0.91–2.55)	0.111		
Urinary tract abnormalities	1.31 (0.89–1.93)	0.170		
Indwelling urinary device	0.74 (0.50–1.10)	0.133	0.97 (0.61–1.54)	0.895
Site of infection (CO-HAI)	1.44 (0.98–2.12)	0.063	1.15 (0.74–1.80)	0.531
Previous antimicrobial use (3 months)				
Fluoroquinolones	2.52 (1.42–4.70)	0.001	2.43 (1.25–4.69)	0.009
Non-antipseudomonal penicillins	1.12 (0.74–1.72)	0.600		
Antipseudomonal penicillins	1.78 (0.98–3.37)	0.059	1.93 (0.96–4.10)	0.063
Cephalosporins	1.90 (1.27–2.88)	0.002	2.14 (1.35–3.41)	0.001
Monobactam (aztreonam)	0.63 (0.02–24.8)	0.777		
Carbapenems group 1[a]	1.90 (0.89–4.42)	0.097	1.27 (0.53–3.05)	0.595
Carbapenems group 2[a]	1.78 (1.01–3.27)	0.045	2.08 (1.03–4.20)	0.040
Aminoglycosides	1.87 (0.54–8.96)	0.341		
Clinical presentation				
Pitt score >2	1.80 (1.20–2.74)	0.005		
Septic shock	1.17 (0.66–2.11)	0.592		
ICU admission required	1.17 (0.71–1.95)	0.547		
Irritative urinary symptoms	0.95 (0.63–1.46)	0.830		
Renal pain	1.02 (0.55–1.94)	0.947		
Prostate pain in DRE	0.38 (0.07–1.64)	0.201		
Temperature >38 °C	0.61 (0.34–1.06)	0.082		
Leucocytes (10^3/μL)	1.00 (0.98–1.02)	0.994		
Micro-organism[b]				
Escherichia coli	3.13 (2.11–4.69)	<0.001	3.34 (2.02–5.53)	<0.001
Klebsiella pneumoniae	0.92 (0.58–1.46)	0.714		
Proteus spp.	0.69 (0.28–1.70)	0.407		
Other Enterobacterales	0.40 (0.22–0.72)	0.002	0.58 (0.29–1.16)	0.123
Pseudomonas aeruginosa	0.29 (0.15–0.57)	<0.001	0.32 (0.15–0.70)	0.004
Enterococcus spp.	0.42 (0.17–1.01)	0.253		

MDR, multidrug resistant; OR, odds ratio; CI, confidence interval; UTI, urinary tract infection; CO-HAI, community-onset healthcare-associated infection; ICU, intensive care unit; DRE, digital rectal examination.
[a] Group 1 carbapenems included ertapenem; group 2 carbapenems included imipenem and meropenem.
[b] The reference category for each uropathogen was the absence of such uropathogen.

Conversely, *P. aeruginosa* was significantly associated with a lower ratio of MDR episodes, despite having the highest percentage of XDR isolates among all uropathogens (12.2% vs 1.6%; $P = 0.003$). This result might be explained by the fact that *P. aeruginosa* is intrinsically resistant to a wide range of antimicrobials and that it can easily develop further antibiotic resistance through chromosomal mutations or the horizontal acquisition of resistant determinants. This is the case of the so-called high-risk clones (such as ST175 or ST235) which are associated with XDR phenotypes and are highly disseminated in the healthcare system, posing a growing threat in hospitals worldwide [18].

Antibiotic consumption exerts a selective pressure and has an impact on the normal microbiota, promoting colonization by MDR organisms. As a consequence, it has been widely reported that antimicrobial exposure is associated with increased

Table IV
Univariate and multivariate analysis of parameters associated with non-clinical stability 48–72 h after onset of BUTI

Variable	Unadjusted OR		Adjusted OR	
	(95% CI)	*P*	(95% CI)	*P*
Baseline features				
Gender (female)	0.95 (0.57–1.57)	0.846		
Age (years), median (IQR)	1.00 (0.98–1.02)	0.658		
Charlson index, median (IQR)	0.97 (0.89–1.07)	0.698		
Any underlying disease	0.84 (0.40–1.77)	0.638		
Diabetes mellitus	1.16 (0.69–1.95)	0.571		
Chronic renal failure	1.19 (0.72–1.99)	0.494		
Chronic pulmonary disease	0.75 (0.35–1.59)	0.466		
Cardiovascular disease	1.16 (0.69–1.95)	0.571		
Chronic liver disease	1.03 (0.38–2.81)	0.923		
Vascular/degenerative brain disease	0.94 (0.52–1.70)	0.852		
Malignant disease	0.77 (0.47–1.26)	0.296		
Immunosuppressive therapy	1.01 (0.59–1.73)	0.952		
Recurrent UTI (>2 episodes/year)	1.40 (0.78–2.51)	0.262		
Urinary tract abnormalities	1.23 (0.76–1.98)	0.398		
Indwelling urinary devices	0.90 (0.56–1.47)	0.683		
Community-onset HCA acquisition	1.21 (0.75–1.95)	0.437	1.26 (0.74–2.13)	0.393
Previous antibiotic use (3 months)	0.79 (0.47–1.33)	0.378		
Clinical presentation				
Pitt score >2	1.86 (1.15–3.02)	0.013		
Septic shock	3.15 (1.73–5.73)	<0.001	3.32 (1.78–6.22)	<0.005
ICU admission required	2.47 (1.43–4.24)	0.002		
Irritative urinary symptoms	0.84 (0.49–1.44)	0.541		
Renal pain	0.73 (0.31–1.69)	0.474		
Prostate pain during DRE	1.44 (0.29–7.28)	0.643		
Temperature >38 °C	0.68 (0.36–1.27)	0.237		
Leucocytes (10^3/μL), median (IQR)	1.02 (0.99–1.04)	0.232		
Micro-organism				
Escherichia coli	1.12 (0.69–1.81)	0.646		
Klebsiella pneumoniae	1.78 (1.05–3.03)	0.037	1.90 (1.06–3.40)	0.031
Other Enterobacterales	0.43 (0.17–1.13)	0.072	0.52 (0.19–1.41)	0.196
Pseudomonas aeruginosa	0.44 (0.15–1.27)	0.113	0.45 (0.14–1.40)	0.169
Proteus spp.	2.26 (0.88–5.80)	0.110		
Enterococcus spp.	0.44 (0.10–1.93)	0.277		
MDR profile	2.15 (1.26–3.69)	0.004	1.66 (0.92–2.97)	0.090
Antibiotic empirical treatment				
Fluoroquinolones	1.52 (0.71–3.25)	0.290		
Non-antipseudomonal penicillins	0.68 (0.35–1.32)	0.258		
Antipseudomonal penicillins	0.65 (0.34–1.24)	0.194		
Cephalosporins	1.03 (0.62–1.73)	0.894		
Carbapenems	1.21 (0.74–1.96)	0.446		
Group 1[a]	1.41 (0.67–3.01)	0.371		
Group 2[b]	1.06 (0.64–1.78)	0.806		
Aminoglycosides	1.17 (0.54–2.56)	0.671		
Monobactam (aztreonam)	3.36 (0.74–15.3)	0.149		
Inappropriate empirical antibiotic therapy	1.61 (0.92–2.84)	0.106	1.87 (1.02–3.54)	0.046

BUTI, bacteraemic urinary tract infection; OR, odds ratio; CI, confidence interval; IQR, interquartile range; UTI, urinary tract infection; ICU, intensive care unit; DRE, digital rectal examination; MDR, multidrug resistant.
[a] Included ertapenem.
[b] Included imipenem and meropenem.

antimicrobial resistance at both community and individual levels [19–21]. In our study, the MDR profile was associated with prior use of fluoroquinolones, cephalosporins, and group 2 carbapenems (imipenem or meropenem) but not group 1 carbapenems (i.e. ertapenem).

Consistent with our data, exposure to fluoroquinolones has been linked to the emergence of MDR- and carbapenem-resistant GNB [22,23]. Several factors might explain this association. First, overuse of fluoroquinolones can induce high expression of chromosomal efflux pumps, which actively

Table V
Univariate and multivariate analysis of factors related to length of hospital stay after onset of bacteraemic urinary tract infection

Variable	Bivariate analysis		Multivariate analysis	
	Median length of hospital stay, days (IQR)	*P*-value	Median difference in hospital stay, days (95% CI)	*P*-value
Gender		0.511		
Male	11.00 (8.00—19.00)			
Female	12.50 (8.00—20.00)			
Age (years)	$P = -0.104$	0.035	−0.06 (−0.16 to 0.03)	0.209
Charlson comorbididty index	$P = 0.054$	0.272	0.01 (−0.43 to 0.46)	0.953
Any underlying disease				
No	11.00 (7.00—21.00)	0.649		
Yes	12.00 (8.00—20.00)			
Diabetes mellitus				
No	12.00 (7.00—19.00)	0.137		
Yes	12.00 (8.00—23.00)			
Chronic renal failure				
No	12.00 (7.00—19.00)	0.328		
Yes	12.00 (8.00—21.00)			
Chronic pulmonary disease		0.486		
No	12.00 (8.00—20.00)			
Yes	10.50 (7.00—18.50)			
Cardiovascular disease				
No	11.00 (7.00—19.00)	0.084		
Yes	14.00 (8.00—21.00)			
Chronic liver disease				
No	12.00 (8.00—19.00)	0.203		
Yes	16.00 (7.00—31.00)			
Vascular/degenerative brain disease				
No	12.00 (7.00—20.00)	0.381		
Yes	13.00 (8.00—20.00)			
Malignant disease				
No	13.00 (8.00—21.00)	0.019		
Yes	10.00 (7.00—17.00)			
Immunosuppressive therapy				
No	11.50 (8.00—19.00)	0.277		
Yes	13.50 7.00—22.00)			
Recurrent UTI (>2 episodes/year)				
No	12.00 (8.00—21.00)	0.178	−0.47 (−3.48 to 2.54)	0.758
Yes	10.50 (7.00—18.00)			
Indwelling urinary devices				
No	11.00 (7.00—17.00)	0.014		
Yes	13.00 (8.00—21.00)		1.01 (−1.41 to 3.42)	0.412
Site of acquisition				
Community-onset HAI acquisition	9.50 (7.00—14.00)	<0.001		
Hospital-acquired	16.00 (10.00—29.50)		6.73 (4.32—9.14)	<0.001
Previous antibiotic use (3 months)				
No	11.00 (7.00—17.00)	0.097		
Yes	12.00 (8.00—21.00)		0.35 (−2.25 to 2.95)	0.794
Pitt score				
≤2	11.00 (7.00—17.00)	<0.001		
>2	14.00 (9.50—22.00)			
Septic shock				
No	11.00 (7.00—18.00)	<0.001		
Yes	17.00 (10.00—23.00)		5.14 (1.91—8.36)	0.002
ICU admission required				
No	11.00 (7.00—17.00)	<0.001		
Yes	21.00 (12.00—38.00)			

(*continued on next page*)

Table V (*continued*)

Variable	Bivariate analysis		Multivariate analysis	
	Median length of hospital stay, days (IQR)	*P*-value	Median difference in hospital stay, days (95% CI)	*P*-value
MDR profile				
Non-MDR	10.00 (7.00–15.50)	<0.001		
MDR	13.00 (8.00–22.00)		3.08 (0.56–5.61)	0.017
Escherichia coli				
No	13.00 (8.00–22.00)	0.036		
Yes	11.00 (7.00–17.00)		0.95 (−3.14 to 5.04)	0.648
Klebsiella pneumoniae				
No	11.00 (7.00–18.00)	0.010		
Yes	14.00 (9.00–22.00)		2.44 (−1.78 to 6.65)	0.256
Other Enterobacterales				
No	12.00 (8.00–20.00)	0.148		
Yes	11.00 (6.50–16.00)		0.39 (−4.06 to 4.84)	0.863
Pseudomonas aeruginosa				
No	12.00 (8.00–20.00)	0.126		
Yes	15.00 (9.00–28.00)		4.80 (−0.13 to 9.72)	0.056
Proteus spp.				
No	12.00 (8.00–20.00)	0.713		
Yes	11.00 (5.00–22.00)			
Enterococcus spp.				
No	12.00 (7.50–19.50)	0.158		
Yes	14.00 (9.50–35.50)		5.81 (−0.16 to 11.78)	0.065
Inappropriate empirical antibiotic therapy				
No	11.00 (8.00–19.00)	0.085		
Yes	14.00 (8.00–22.00)		−2.84 (−2.84 to 2.79)	0.987

IQR, interquartile range; CI, confidence interval; UTI, urinary tract infection; HAI, healthcare-associated infection; ICU, intensive care unit; MDR, multidrug resistant.
In the bivariate analyses, data are presented as median (interquartile range) unless otherwise specified. The strength of association between quantitative continuous variables and median hospital stay was measured using the Spearman correlation coefficient (rho). In the multivariate analyses, differences are expressed as differences in median values (95% CI).

remove different antibiotics, including carbapenems, leading to MDR profile [20,22,23]. Moreover, fluoroquinolones have also been associated with the expansion of successful international MDR high-risk clones of *P. aeruginosa* [21,24,25], Entero-bacterales, MRSA and *C. difficile* [22,23]. In fact, it has been suggested that fluoroquinolones have shaped the evolution of such clones over the last three decades, promoting the acquisition of characteristic mutations in quinolone resistance-determining regions (QRDRs) that are energetically beneficial, facilitating the acquisition of other resistance genes without significant fitness cost [23]. Furthermore, horizontally acquired quinolone-resistance genes are often encoded on plasmids carrying other antimicrobial resistance genes such as ESBLs [22,23].

As for cephalosporins, there has been evidence of a link between cephalosporin use and the emergence of MDR organisms for decades [26]. Cephalosporins have been associated with selection of penicillin-resistant pneumococci, meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococcus, MDR *P. aeruginosa*, ESBL-producing Enterobacterales, and *C. difficile* [26,27].

Several studies support the correlation between previous carbapenem consumption and higher rates of MDR and carbapenem resistance [21,28]. However, the role of ertapenem in selection of antibiotic resistance is still a subject of debate. Ertapenem is classified as a group 1 carbapenem with weak activity against non-fermenting GNB such as *Pseudomonas* and *Acinetobacter* species [29]. In this respect, several ecological studies have observed that its consumption is not related to an increase in carbapenem-resistant *P. aeruginosa*, suggesting a more favourable ecological impact [30–32]. However, others suggest that ertapenem may select resistance to group 2 carbapenems despite its lack of anti-pseudomonal activity [21,33]. Some in-vitro models showed that ertapenem selected for cross-resistance to other carbapenems [34,35], although this phenomenon probably does not occur at physiological concentrations of ertapenem [35]. In addition, ertapenem damage to the gastrointestinal microbiome may allow for the selection and spread of resistant strains [21]. With respect to Enterobacterales, several studies suggest that the introduction of ertapenem was not associated with changes in antimicrobial resistance in *E. coli*, *K. pneumoniae*, and other Entero-bacterales [36–38]. A recent review of carbapenem stewardship with ertapenem also suggested that ertapenem consumption was not associated with group 2 carbapenem-resistant Enterobacterales or *P. aeruginosa* [38]. Consistent with these studies, our results suggest that ertapenem could be an option in stewardship programmes to spare the use of group 2 carbapenems without increasing antibiotic resistance. However, no *Acinetobacter* episodes were included in our cohort,

and the number of *P. aeruginosa* episodes was small, so that our results concerning the effects of ertapenem on resistance ecology should be extrapolated mainly to Enterobacterales.

MDR infections pose a threat in hospitals and long-term care facilities. In the present study, we evaluated the clinical impact of MDR on our cohort of patients with healthcare-associated BUTI. MDR was associated with a higher risk of receiving inappropriate empiric antimicrobial treatment and longer duration of hospitalization. These results are similar to previous studies in which MDR infections were associated with higher costs and longer hospitalization [4,6]. In our study, no differences in clinical cure were observed 48 h after the onset of bacteraemia or at hospital discharge, but hospital stay was significantly longer in MDR infections. In a recent systematic review and meta-analysis of the economic and clinical burden of MDR in HAIs, MDR infections were associated with increased length of stay, increased hospital costs, and increased hospital mortality [39]. In a recent systematic study analysing the global burden associated with antimicrobial resistance in 2019, it was estimated that the burden of antimicrobial resistance was 4.95 million deaths worldwide, 1.27 million of which were attributable to antibiotic resistance [2]. The clinical burden of MDR infections can be influenced by many factors including the affected population and source of infection. With respect to host factors, in our cohort, only HAI episodes were included, and no significant differences in population ageing, demographics, or epidemiological factors were observed between groups. With respect to the source of infection, only UTIs were included, which are considered a low-risk source of infections, with generally lower mortality than other sources [40,41]. This could explain, at least in part, why we did not find differences in clinical cure in our cohort. However, other studies that attempted to estimate the impact of MDR on the outcome of healthcare-associated infections also observed that the additional effect of antimicrobial resistance on clinical outcome was low or non-existent [42,43].

Of note, the present study was conducted in Spain, in southern Europe, which is a country with high rates of MDR-GNB [7,44]. According to the Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net), MDR rates are higher in southern and south-eastern Europe than in northern Europe [44]. Indeed, a previous meta-analysis showed that there was a greater link between consumption and antibiotic resistance in southern European countries than in other regions, suggesting that efforts to reduce antibiotic consumption should be intensified in this area [19]. The high rates of MDR observed in our study highlight the need to promote strategies to reduce antimicrobial resistance, including public health actions, infection prevention and control, and antimicrobial stewardship programmes.

This study has several limitations. First, we included only bacteraemic UTIs and our data may be influenced by certain successful clones, such as *E. coli* ST131, which are more closely linked to a urinary source than to others [45]. Therefore, our results may not be generalizable to other sources of infection. However, the inclusion of patients with homogeneous criteria (bloodstream infection and urinary source) avoids bias arising from the inclusion of different sources that could interfere in the analysis of outcome measures. Second, as mentioned above, the study was conducted in a country with high rates of MDR GNB and results may have been influenced by local epidemiological variables that do not apply to other settings, such as high prior exposure to antibiotics or different rates of horizontal transmission [6,46]. Moreover, the extremely high proportion of MDR in our cohort may have limited the prediction and adjustment of empirical therapy. Third, due to the observational nature of the study, data related to prior MDR colonization were not systematically collected in patients included in the study. Prior colonization is a stronger predictor of MDR and it might be correlated with the prior use of antimicrobial [46,47]. Fourth, we defined MDR profile according to previous consensus criteria [9]. However, there are currently concerns about the need to improve the existing definitions of MDR, XDR and PDR as they consider all antibiotics equally, irrespective of their applicability, efficacy, and toxicity. As an alternative, other terms have been proposed, such as difficult-to-treat resistant (DTR) infections, defined as resistance to all first-line antibiotics, including all β-lactams and fluoroquinolones [48]. In our cohort, the rate of MDR strains was very high, while the XDR/PDR pattern was not common. Nonetheless, these results are still concerning and pose a threat for the healthcare system. For instance, the rate of MDR ESBL-producing isolates was quite high in our cohort (117/468, 25%). Although most of them did not meet the criteria to be defined as XDR nor DTR infections, they were frequently co-resistant to β-lactamase inhibitor combinations, fluoroquinolones, aminoglycosides, and other antimicrobial agents, thus limiting the therapeutic options and challenging the selection of empirical treatment [6]. Fifth, although we evaluated length of hospital stay, no economic cost analyses were performed. Cost studies to assess the economic burden of MDR infections would have been useful. Moreover, dosage of antibiotic was not collected in our study. This information would have been useful to evaluate the prior antibiotic exposure and to evaluate the appropriate antibiotic treatment exposure during the episode. Sixth, the small number of patients with *P. aeruginosa* or *Enterococcus* spp. infection limited our results. Therefore, our data should be extrapolated mainly to Enterobacterales infections. Finally, our study has other limitations typical of observational studies. Although the cases should be consecutive, we were unable to assess this aspect and the possibility of selection bias cannot be ruled out. Moreover, post-hoc analysis looks back at data collected for different purposes, and might limit the ability to draw strong causal inferences. Nevertheless, several strengths of this study should be highlighted. All participating centres had expertise in investigating patients with bacteraemia and the data were recorded by trained investigators, which improves data quality. In addition, microbiological analyses were performed to identify the resistance mechanism involved, such as ESBL or carbapenemase production. Finally, this large cohort of patients with healthcare-associated BUTIs allowed us to evaluate variables associated with MDR in patients with this profile.

In conclusion, in our prospective cohort study exploring risk factors associated with the MDR profile in healthcare-associated BUTI, prior exposure to fluoroquinolones, cephalosporins, and group 2 carbapenems (meropenem and imipenem) was associated with an MDR profile, but no statistical association was observed with ertapenem or other antibiotic groups. With respect to outcome measures, MDR episodes were not associated with a less frequent clinical cure either 48—72 h

after onset of bloodstream infection or at hospital discharge. The MDR profile, however, was independently associated with longer hospital stay.

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Conflict of interest statement

J.L.D.P. has received payment or honoraria for educational activities from MSD, Gilead, Advanz, Menarini, Pfizer, and Angelini. R.P. and M.C. are employees of MSD Spain. R.C. has participated in educational programmes organized by Menarini, MSD and Shionogi. A.O. has participated in educational programmes organized by MSD Pfizer and Shionogi and research projects funded by MSD and Shionogi. P.R.G. has participated in educational programmes organized by MSD, Shionogi, and Menarini. J.P.H. has received consulting fees and/or participated in educational programmes organized by Pfizer, Angelini, Menarini, MSD, Zambon, Tillots, Advanz, Alifax and GSK; and has participated in advisory boards organized by TFT Pharmaceuticals. The other authors have no conflicts to declare.

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Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki. The study was approved by the Clinical Research Ethics Committee of the Hospital del Mar (registration no. 2016/6957/I) and by the local ethics committees of the participating centres. All patients provided written informed consent at screening. Patients unable to provide informed consent could be included with the signature of a relative or legal representative.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2024.05.020.

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