Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Hospital Infection 120 (2022) 48–56

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Nosocomial outbreak of monoclonal VIM carbapenemase-producing *Enterobacter cloacae* complex in an intensive care unit during the COVID-19 pandemic: an integrated approach

C. Mullié [a,b,*], D. Lemonnier [c,**], C.C. Adjidé [a], J. Maizel [d], G. Mismacque [c], A. Cappe [e], T. Carles [e], M. Pierson-Marchandise [f], Y. Zerbib [d]

[a] *Laboratoire Hygiène Risque Biologique & Environnement, CHU Amiens Picardie, Amiens, France*
[b] *Laboratoire AGIR UR UPJV 4294, Université de Picardie Jules Verne, Amiens, France*
[c] *Unité d'Hygiène et d'Epidémiologie Hospitalière, CHU Amiens Picardie, Amiens, France*
[d] *Service de Médecine Intensive et Réanimation, CHU Amiens Picardie, Amiens, France*
[e] *Département de Pharmacie Clinique, CHU Amiens Picardie, Amiens, France*
[f] *Service Prévention, Evaluations, Vigilances et Amélioration des Pratiques, CHU Amiens Picardie, Amiens, France*

ARTICLE INFO

Article history:
Received 2 October 2021
Accepted 24 November 2021
Available online 30 November 2021

Keywords:
Outbreak
Enterobacter cloacae complex
Healthcare-associated infection
Fourier-transform infra-red spectroscopy
Integrated approach
Carbapenemase

SUMMARY

Background: An outbreak of VIM carbapenemase-expressing *Enterobacter cloacae* complex occurred between March and October 2020 in an intensive care unit (ICU) of a tertiary care and teaching hospital in France. At the same time, the hospital was facing the COVID-19 first wave.

Aim: To describe the management of an outbreak caused by a VIM-producing *Enterobacter cloacae* complex strain during the COVID-19 pandemic in an ICU and to show the importance of an integrated approach.

Methods: A multi-focal investigation was conducted including descriptive and molecular epidemiology, environmental screening, and assessment of infection prevention and control measures.

Findings: A total of 14 cases were identified in this outbreak with a high attributable mortality rate (85.7%). The outbreak management was coordinated by a crisis cell, and involved the implementation of multi-disciplinary actions such as: enhanced hygiene measures, microbiological and molecular analysis of patients and environmental *E. cloacae* complex strains, and simulation-based teaching. All 23 *E. cloacae* complex strains isolated from patients and environment samples belonged to multi-locus sequence type ST78 and carried *bla*-$_{VIM4}$ gene. Using Fourier transform infrared spectroscopy, all but two isolates were also found to belong to a single cluster. Although the source of this outbreak could not be pinpointed, the spread of the strain was controlled thanks to this multi-focal approach and multi-disciplinary implementation.

* Corresponding author. Address: Laboratoire Hygiène Risque Biologique & Environnement, CHU Amiens Picardie, Amiens, France. Tel.: +33 3 22 08 70 99.
** Corresponding author. Address: Unité d'Hygiène et d'Epidémiologie hospitalière, CHU Amiens Picardie, Amiens, France. Tel.: +33 3 22 06 82 22.
E-mail addresses: mullie-demailly.catherine@chu-amiens.fr (C. Mullié), lemonnier.delphine@chu-amiens.fr (D. Lemonnier).

https://doi.org/10.1016/j.jhin.2021.11.017

Conclusion: This investigation highlighted the usefulness of Fourier transform infra-red spectroscopy in the rapid typing of outbreak strains as well as the importance of an integrated approach to successfully fight against multidrug-resistant micro-organism dissemination and healthcare-associated infections.

Introduction

Multidrug-resistant (MDR) bacteria have become a major worldwide public health challenge and hospitals are now increasingly faced with management of local outbreaks involving such pathogens. Especially, intensive care units (ICUs) provide an ideal background for outbreaks caused by MDR bacteria among which carbapenemase-producing Entero-bacterales (CPE) may be found [1,2]. Amid CPE involved in ICU outbreaks, VIM producers have been reported worldwide, and described as especially difficult to control [2]. In France, few outbreaks involving these pathogens have been reported [3]. However, the number of VIM strains identified by the national referent centre (Centre National de Référence-CNR) has been in constant increase since 2012 [4]. In 2017, the national prevalence for *E. cloacae* with carbapenem resistance was $<$0.01%, among 185 isolates [5]. Locally, few cases of infections due to VIM-producing strains were registered: one or two per year from 2016 till 2018 and five cases in 2019, without any obvious epidemiologic link found between them. Infection prevention and control (IPC) measures employed during the COVID-19 pandemic have been implicated in outbreaks with MDR bacteria [6]. In particular, use and misuse of personal protective equipment (PPE) such as gloves or gowns have been reported to be contributory factors [7]. The likely origin of outbreaks is not always easy to pinpoint, but common sources are index patients with a history of hospitalization abroad, contaminated instruments, and/or environmental reservoirs [1]. CPE outbreaks in ICUs usually require a combination of IPC measures to achieve control, including screening of patients, use of contact precautions, staff education, enhanced environmental cleaning and disinfection, cohorting of patients and staff as well as proper antimicrobial stewardship. Investigation and management of outbreaks require close cooperation and communication between all involved healthcare workers [8].

In this retrospective study, we describe the management of an outbreak caused by a VIM-producing *Enterobacter cloacae* complex (ECC) strain during the 2020 COVID-19 pandemic in an ICU, including the first reported use of Fourier-transform infrared spectroscopy for the prospective typing/clustering of outbreak isolates.

Methods

Case definition and series

From March through October 2020, patients colonized/infected with VIM-producing ECC were identified in one of the five ICUs at a tertiary care and teaching hospital in France. This care unit houses 16 beds for adult patients with an internal medicine care pathway but, at the time of this outbreak, was not a COVID-19-dedicated ward. Demographic data included age and gender. Comorbidities were collected. On the first day of ICU admission, severity and organ failure scores (Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA)) were computed. Organ support requirement and mortality in the ICU were recorded. Classification between infection and colonization as well as cause of death were prospectively determined in medical meetings with independent clinicians.

Initially, suspected cases were identified through peri-rectal screening undertaken on admission, and weekly thereafter, in accordance with French guidelines as well as local routine practice [9]. VIM-producing ECC isolates were characterized by identification of the suspected isolates using matrix-assisted laser desorption—ionization time-of-flight mass spectrometry (MALDI Biotyper 2.2; Bruker Daltonik GmbH, Bremen, Germany) and carbapenemase production ascertained using Xpert carba-R® kit (Cepheid, Sunnyvale, CA, USA) and/or Resist-5 OOKNV® immunoassay kit (Coris Bioconcept, Gembloux, Belgium). Antimicrobial susceptibility was assessed according to the EUCAST guidelines [10]. A case was defined as an ECC isolate positive for VIM production obtained from either a clinical or a surveillance sample from a patient with a negative admission screening culture and admitted in the ICU on or after March 1st, 2020.

Causal analysis and environmental assessment

After detection of the third VIM-producing ECC isolate, the standard institutional procedure related to IPC measures was implemented and maintained until the last positive case left. This procedure includes:

- contact precautions for colonized/infected patients and 'at-risk' patients (i.e. patients treated in the same ward) such as allocation to single rooms, protective gowns for all staff interactions with the patient or their proximal environment, enhanced handwashing practices but no systematic glove wearing [9];
- testing and follow-up of positive and 'at-risk' patients [9];
- terminal cleaning followed by room disinfection with hydrogen peroxide vapour after patient exit;
- cohorting or care organization based on a go-forward approach [9];
- activation of a crisis cell including the general leadership of the hospital [9].

Complementary investigations were conducted to try to identify a possible contamination source and better characterize the bacterial strains involved, as described below.

Environmental assessment following the outbreak

Following a cause analysis scheme previously set up, each patient room was investigated by multiple swabbing of surfaces (Figure 1 and Supplementary Table S1) using Sigma transwab-liquid Amies devices (Medical Wire & Equipment, Corsham, UK) followed by seeding on Columbia Sheep blood agar (Becton–Dickinson, Le Pont de Claix, France), Drigalski (Becton–Dickinson) and Carbasmart (bioMérieux SA, Marcy l'Étoile, France) media and an overnight incubation at 36 ± 2 °C. When feasible, a 25 cm^2 (5 × 5 cm template) surface was sampled; when not, the whole surface was sampled. Additionally, sink drains removed from the ICU rooms, samples collected from shared medical devices, and samples collected in common areas of the affected unit were examined for the presence of carbapenemase-producing bacteria (Supplementary Table S2).

Enterobacter cloacae complex whole-genome sequencing, MLST sequence-type determination, and Fourier transform infra-red (FTIR) spectroscopy typing

Thirteen patient strains along with 10 strains recovered from environmental samples were submitted to high-throughput whole-genome sequencing using the Illumina technique, as previously described [11]. Multi-locus sequence typing (MLST) sequence-type (ST) determination was performed using the MLST scheme established by Miyoshi-Akiyama *et al.* [12]. Clustering of the same 23 isolates was also carried out using FTIR (IR-Biotyper®, Bruker Daltonik). Another ECC strain identified as only expressing an extended-spectrum β-lactamase (ESBL) was added to the panel and served as outlier. Briefly, isolates were subcultured twice for 18 h at 36 ± 2 °C on Plate Count Agar (PCA) (bioMérieux SA) and then processed using IR Biotyper kit according to the manufacturer's recommendations. Spectra were acquired and processed by OPUS software v8.2 (Bruker Optics GmbH). Data from the area corresponding to polysaccharides (1300–800/cm) were used for the analysis of differences between isolates. Dendrograms were built by IR Biotyper Client Software v3.0 (Bruker Daltonik) using Euclidian distance and average linkage clustering method. This method has been previously described and proposed as useful in retrospectively typing outbreak isolates [13,14].

Ethics

This study was approved by the local ethics commission and registered by the CNIL (Commission Nationale Informatique et Libertés) under the number PI2021_843_0187.

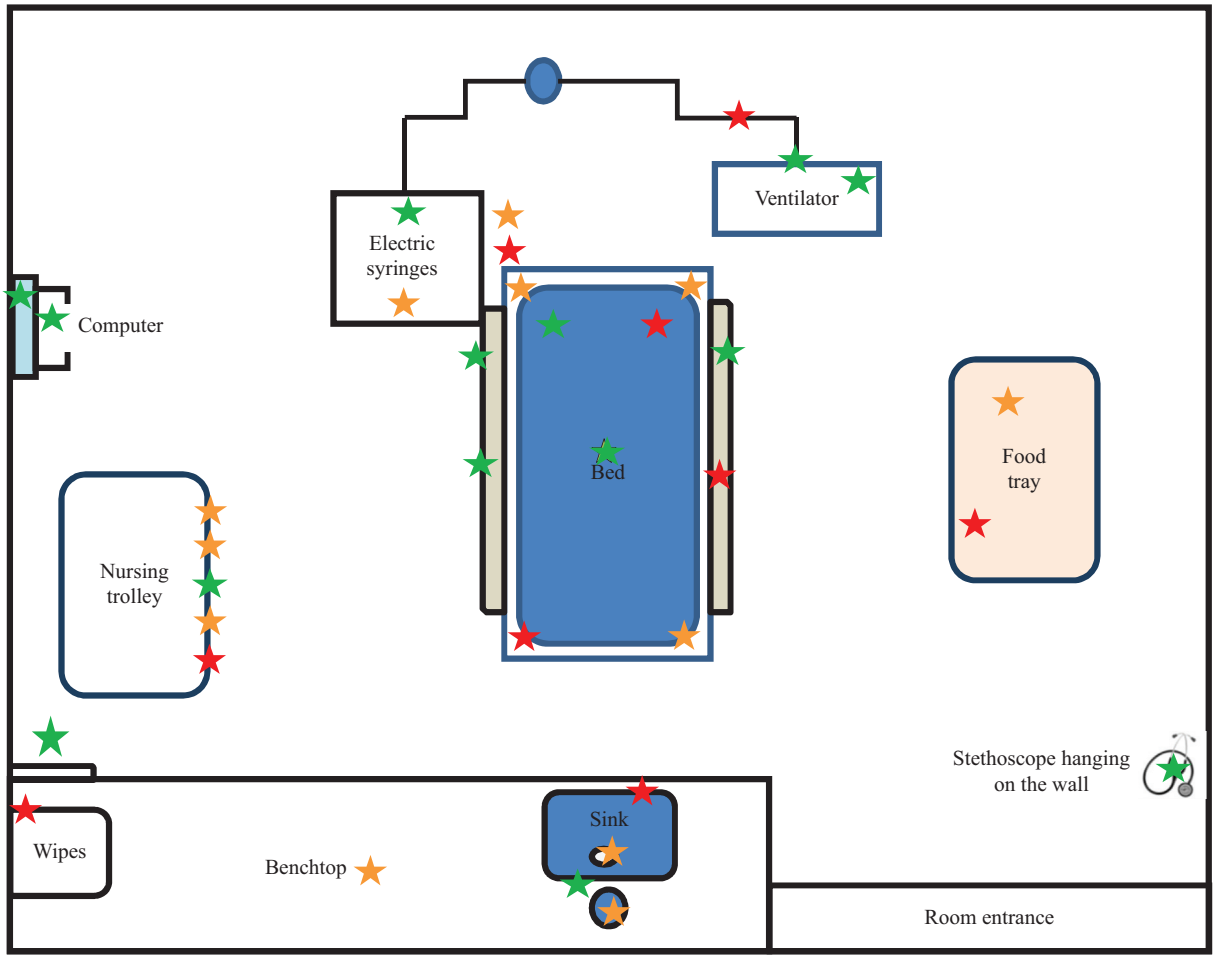

Figure 1. Spatial distribution of sampling points in intensive care unit room. Green star: no pathogens found; red star: *E. cloacae* VIM; orange star: other pathogens found.

Table I
Clinical characteristics of VIM-producing *Enterobacter cloacae* complex patients

Variable	Case patients ($N = 14$)
Male	9 (64%)
Age (years)	62 (58.3–67)[a]
Body mass index (kg/m^2)	30.9 (29.4–35)[a]
Comorbidities	
Obesity	9 (64.3%)
Hypertension	8 (57.1%)
Diabetes	4 (28.6%)
Cardiovascular disease	3 (21.4%)
Chronic obstructive pulmonary disease	2 (14.3%)
Chronic kidney disease	1 (7.1%)
Malignancies	1 (7.1%)
Simplified Acute Physiology Score II	44 (36.8–50)[a]
Acute respiratory distress syndrome	8 (57.14%)
Severe	7 (87.5%)
Moderate	1 (12.5%)
Support organ failure	
Invasive mechanical ventilation	14 (100%)
Vasopressor	12 (85.7%)
Renal replacement therapy	6 (42.9%)
Mechanical ventilation (days)	27.5 (21–30)[a]
Length of stay in ICU (days)	30 (24.8–35)[a]
Length of stay in hospital (days)	32 (26–36.3)[a]
Delay between ICU admission and rectal carriage (days)	17 (14.5–27.3)[a]
Delay between ICU admission and infection (days)	17 (10–22.5)[a]

ICU, intensive care unit.
[a] Median (interquartile range).

Results

Case-finding and series

Over the six-month outbreak period, 410 patients were admitted to the ICU. Among them, 19.3% were affected by COVID-19. VIM-producing ECC strains were isolated from 14 patients (3.4%); their characteristics and comorbidities are presented in Table I. Seven were infected by SARS-CoV-2. The index case was a woman aged 59 years, whose admission on March 7th was due to her COVID-19-related acute respiratory distress syndrome (ARDS). For this first patient, a VIM-producing ECC strain was detected in a bronchoalveolar sample on March 24th. Due to the patients' age, major comorbidities were highly prevalent. The main reason for ICU admission of these 14 patients was acute respiratory failure, specifically COVID-19-related ARDS. They had more frequently active infection (78.6%) rather than bacterial colonization (21.4%). Ventilator-associated pneumonia and septic shock were the most frequent clinical presentations in ECC-positive patients (90.9% and 72.7%, respectively). The mortality rate was high (seven patients, 50%) and attributable to the nosocomial infection in 85.7% of the cases.

At the time of VIM-producing ECC-related infection, patients had previously received a median of two different antibiotics. Empiric antibiotic treatment was efficient in only 35.7% (Supplementary Table S3). Therefore, antibiotherapy was adapted and cefiderocol prescribed to five patients (Supplementary Table S4).

Environmental investigation

A total of 1246 samples were analysed. The first round of sampling held in April 2020 (Figure 2) yielded no CPE-positive cultures. In the second round of sampling (September 2020), no positive samples were recovered on medical devices shared for the care of all patients housed in the ICU. The only samples positive for VIM-producing ECC were harvested from the room housing a patient harbouring the bacteria at the time of sampling (nine samples) and an empty room at the time of sampling (one sample). Bacterial isolates cultivated from sink drains did not include any ECC strain. However, a VIM-producing *Pseudomonas aeruginosa* strain was recovered from the sink drain of a patient room. This room was not the same as the ones in which VIM-producing ECC carriers had been housed.

Enterobacter cloacae complex typing and clustering

With a cut-off value set at 0.159, IR-biotyping results led to the assignment of all but two VIM-positive ECC isolates in the single cluster IV (Figure 3) [15]. The outlier strain was successfully recognized and formed a specific pure cluster (Cluster III).

MLST typing revealed that all 23 isolates belonged to ST78 whereas the chosen outlier belonged to ST66. Complete genome sequencing allowed for the identification of bla_{VIM-4} carriage in all environmental and clinical isolates.

Outbreak management

The crisis management cell was activated after the discovery of the third case. Over the outbreak period, ten meetings were organized, including the hospital executive management board six times. These meetings enabled adapted and concerted decisions to be made and granted the means to implement appropriate measures. The coordinated timelines of cases and all instated measures are presented in Figure 2. Several times during this epidemic, a new case occurred while no other case was hospitalized in the unit. Sometimes, a new case was detected several weeks after the exit of the previous ECC carrier from the ICU (Figure 2).

Usual IPC measures were the first concern, including improving hand hygiene and supporting ICU staff in strict application of contact precautions. Medical and paramedical ICU teams were involved in the assessment and improvement of their own practices, daily supported by IPC staff. The results of these evaluations revealed gaps in hand hygiene practices as well as misuse of PPE. These deficiencies were favoured by the heavy workload and very real lack of staff encountered in the ICU during COVID-19 epidemic. Various educational tools were used, such as observational audits, personalized infographics, and simulation-based training.

A thorough cleaning and disinfection of the unit was implemented by closing successively each of its two wards and subjecting each one to terminal cleaning followed by airborne d-

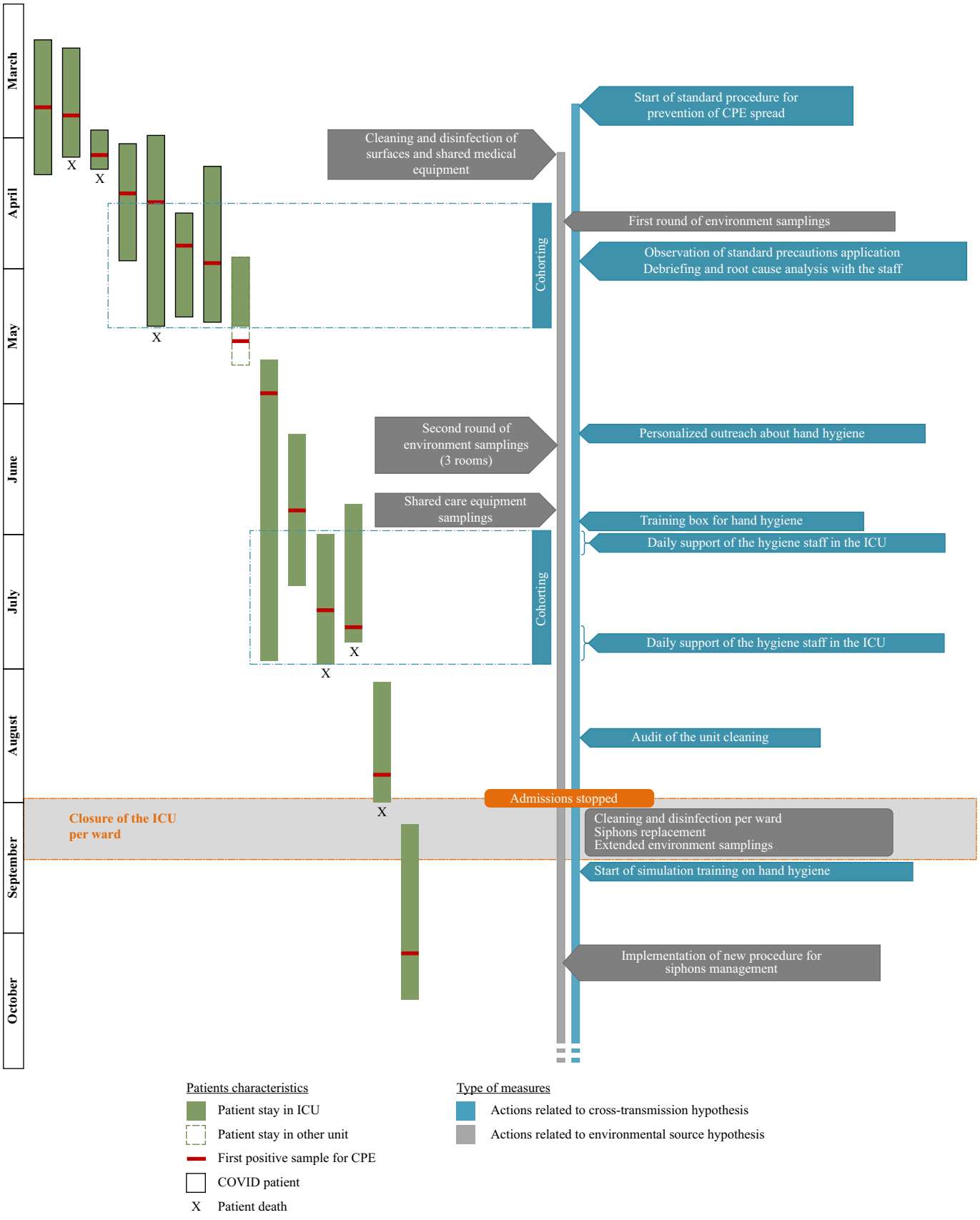

Figure 2. Description of the integrated approach implemented to control this outbreak of carbapenemase-producing Enterobacterales (CPE). Cases are represented in green, with their first positive sample as a red line. Actions are classified into two categories: linked to the control of possible environmental source or linked to the prevention of cross-transmission. The chronology of the implementation of all these actions is represented following the timeline on the left; ICU, intensive care unit.

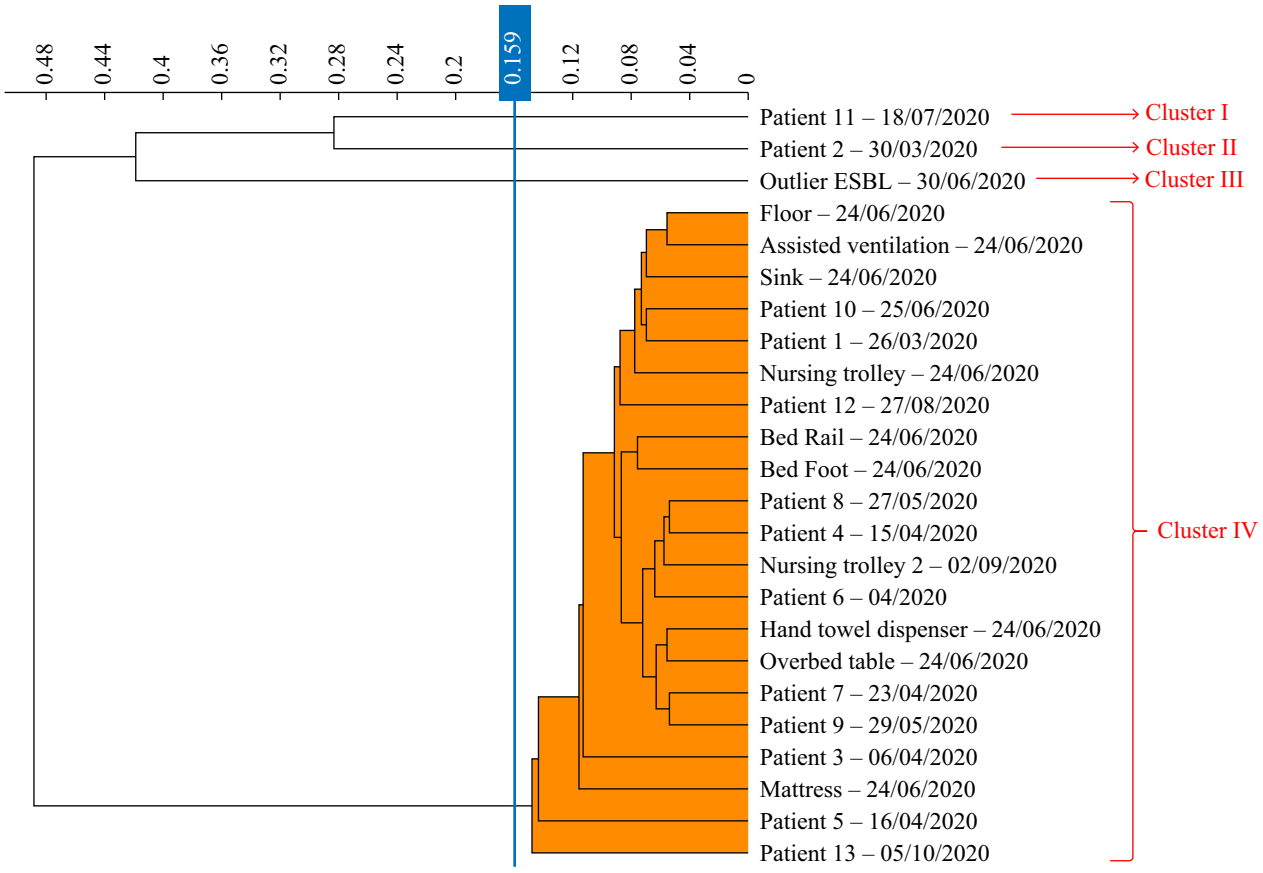

Figure 3. Dendrogram obtained by clustering the Fourier transform infra-red spectra of 23 isolates of *Enterobacter cloacae* complex using the Euclidian distance and average linkage clustering method. For each isolate, source identification is given along with the isolation date. The vertical blue line represents the cut-off value chosen to determine clusters of isolates. Clusters were numbered arbitrarily from top to bottom of the figure.

isinfection of surfaces. In September 2020, after reopening the unit, a new procedure for sink drains decontamination using white vinegar was implemented weekly. A monitoring of the procedure's efficiency was also scheduled by sampling sink drains and looking for the lasting presence of CPE every three months.

Discussion

In the context of the COVID-19 pandemic, we report here a monoclonal outbreak of VIM-producing ECC with a high attributable mortality rate. This high rate is likely linked to COVID-19 co-infections as it has been estimated that secondary infections account for around 50% of fatalities associated with COVID-19 [16–18]. Since the beginning of the COVID-19 pandemic (first local case on February 24th) about 15.2% of patients with an identified CPE carriage have also been infected by SARS-CoV-2. The screening policy did not enable determination of the rate of COVID-19 patients colonized by CPE. However, COVID-19 and CPE co-infections have already been documented [19,20].

Also, the length of stay in the ICU, which is a risk factor for hospital-acquired infections, was extended and influenced by the high proportion of COVID-19-related ARDS [20].

From a clinical point of view, few antibiotic treatments retain activity against VIM-producing micro-organisms: aminoglycosides, intravenous and/or nebulized colistin, tigecycline, and the recently described cefiderocol [21–23]. However, the use of cefiderocol was limited by its availability as a non-marketed product at the time of the outbreak.

To better understand the transmission chain, phenotypic (IR-typing) and molecular typing of environmental and patients' isolates was undertaken. All ECC isolates but the ESBL outlier were found to belong to ST78. As for IR-typing, the ten environmental strains clustered together with 11 clinical isolates out of the 13 tested. Overall, 21 of the 23 (91.3%) ST78 isolates were attributed to a single cluster by IR-typing. The two remaining clinical isolates belonging to the ST78 population were found in separate pure clusters. One of those ST78 isolates (patient 2) displayed phenotypic differences when cultivated on PCA. This could account for variations in IR absorption profiles of membrane carbohydrates between this isolate and the other ST78 ones, leading to a separate clustering by IR-typing as this technique is based on similitudes between carbohydrate absorption spectra. The last isolate (patient 11) had a growth similar to that of other isolates. Therefore, its separate clustering by IR-typing cannot be explained in the same way. Nevertheless, the overall agreement between the reference typing method (MLST) and IR-typing was good, as previously reported [13,15]. This method was used prospectively for the first time in our hospital to help in clustering isolates of an

ongoing VIM-producing ECC outbreak. Moreover, FTIR is cheaper, faster, and does not need highly trained staff to perform. It could therefore be a useful tool in the routine follow-up of bacterial outbreaks, yielding swifter results than MLST.

ECC ST78 has previously been identified as a potential high-risk international clone [24]. Several outbreaks have been reported over the last few years with ECC ST78 strains producing various carbapenemases [25,26]. However, these outbreaks were mostly caused by IMP-positive ECC ST78 strains, whereas bla_{VIM} genes have mostly been reported in *P. aeruginosa*. To the best of our knowledge, this is the first report of an outbreak involving a VIM-positive ECC ST78 clone. A further analysis of core genome single nucleotide polymorphisms might help in determining whether various clades of the ST78 were involved in this outbreak and in identifying multiple introductions and routes of spread, as was previously reported by Harada *et al.* [26]. It could also support or invalidate the separate clustering of two ST78 strains by IR-typing.

Several possible routes of transmission were investigated for this clonal outbreak and preventive/corrective actions implemented. The first one was faulty hand hygiene practices, probably linked to misuse of gloves and gowns, as previously described in outbreak reports [7,27]. An update on good hand hygiene practices was performed using risk management tools such as cause analysis, and infographics created to teach healthcare workers how to put themselves in a reflexive habit regarding their hand hygiene practices. A simulation-based approach to training in healthcare-associated infection prevention and more specifically in hand hygiene was likewise included [28,29]. Since September 2020, the monthly follow-up of an indicator of hydro-alcoholic solution consumption has also been implemented [30]. The possibility of an environmental reservoir was also examined as sinks and sink drains have been reported as possible sources of contaminations, especially in ICUs [31,32]. Indeed, a recent study held in an ICU previously housing COVID-19 patients showed the persistence of Gram-negative bacteria such as *Pseudomonas* spp. and ECC in sinks and sink drains even after terminal cleaning and disinfection [33]. Another study also identified VIM-producing CPE in a case—patient sink drain during an outbreak [34]. Even if the data from the epidemiological investigation in this study do not definitely support a link between colonization/infection of the cases identified in this study and an environmental source, these observations confirm that sinks and sink drains warrant further investigations and management measures to limit MDR persistence and spread. Especially, the identification of VIM-producing *P. aeruginosa* in one sink drain led us to suspect a horizontal plasmid transmission, as previously described in the literature [35,36]. One such management measure is the decontamination of sink drain with acetic acid, which has been reported as efficient in reducing CPE contamination of sink drains as well as the number of CPE-colonized/infected patients [32,37]. After the instatement of such a procedure in the ICU, results obtained from the first round of monitoring samples showed a persistence of VIM-producing *P. aeruginosa* in one patient room. ESBL-producing enterobacteria were also retrieved from two patient rooms as well as in the common sink used by healthcare workers of the ICU.

Upgrades including the addition of automated airborne disinfection of surfaces and medical equipment to manual cleaning to reach sites inaccessible to cleaners were instated [38]. Indeed, this technology has been previously associated with a reduction in environmental contamination and healthcare-associated infections with MDR organisms [39]. The evaluation of existing cleaning practices also allowed us to upgrade the organization between the different actors, and define the exact role of each category of health workers.

Ultimately, the possibility of VIM-producing ECC carriage within the nursing staff was discussed during summer 2020. According to the literature, the link between patient and healthcare worker carriage is not always obvious [40—42]. As no readily available and efficient treatment could have been provided in case of positivity, and since eviction was not an option during the COVID-19 pandemic, especially in an ICU, it was finally decided not to screen the entire staff for VIM-producing ECC carriage. Another limitation of the study was that the number of cases was judged too small and the patients too heterogeneous to perform a case—control study that would have enabled valid conclusions on risk factors from comparisons.

In conclusion, our description of a monoclonal outbreak of VIM-producing ECC and its management reveals how important it is to keep a multi-focal approach to prevent the spread of such strains. Despite the lack of an established origin, the containment of this outbreak was achieved through a multidisciplinary and integrated approach including the ICU clinical staff (descriptive epidemiology and implementation of upgraded IPCs), the hygiene laboratory staff (case detection, environmental sampling, phenotypic and molecular typing), and the IPC unit staff (re-education of healthcare personnel on basic hygiene measures and implementation of upgraded IPCs). Our results also identify FTIR as an interesting alternative to MLST or whole-genome sequencing to quickly, prospectively and cheaply type outbreak isolates. This integrated approach and the associated multi-disciplinary management are keys to a rapid and successful control of outbreaks.

Acknowledgements

The authors would like to acknowledge the ICU, IPC and hygiene laboratory staff for their involvement and contribution in the management of this outbreak.

Conflict of interest statement
None declared.

Funding sources
None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.11.017.

References

[1] French CE, Coope C, Conway L, Higgins JPT, McCulloch J, Okoli G, et al. Control of carbapenemase-producing Enterobacteriaceae outbreaks in acute settings: an evidence review. J Hosp Infect 2017;95:3—45. https://doi.org/10.1016/j.jhin.2016.10.006.
[2] Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. Clin

Microbiol Infect 2014;20:821–30. https://doi.org/10.1111/1469-0691.12719.
[3] Beyrouthy R, Barets M, Marion E, Dananché C, Dauwalder O, Robin F, et al. Novel *Enterobacter* lineage as leading cause of nosocomial outbreak involving carbapenemase-producing strains. Emerg Infect Dis 2018;24:1505–15. https://doi.org/10.3201/eid2408.180151.
[4] Jousset AB, Emeraud C, Bonnin RA, Naas T, Dortet L. Caractéristiques et évolution des souches d'entérobactéries productrices de carbapénémases (EPC) isolées en France, 2012–2020. Bull Epidémiol Hebd 2021;18–19:351–8.
[5] Santé Publique France. Enquête nationale de prévalence des infections nosocomiales et des traitements anti-infectieux en établissements de santé, mai–juin. 2017. Available at: https://www.santepubliquefrance.fr/import/enquete-nationale-de-prevalence-des-infections-nosocomiales-et-des-traitements-anti-infectieux-en-etablissements-de-sante-mai-juin-2017 [last accessed November 2021].
[6] Knight GM, Glover RE, McQuaid CF, Olaru ID, Gallandat K, Leclerc QJ, et al. Antimicrobial resistance and COVID-19: intersections and implications. eLife 2021;10:e64139. https://doi.org/10.7554/eLife.64139.
[7] Ye D, Shan J, Huang Y, Li J, Li C, Liu X, et al. A gloves-associated outbreak of imipenem-resistant *Acinetobacter baumannii* in an intensive care unit in Guangdong, China. BMC Infect Dis 2015;15:179. https://doi.org/10.1186/s12879-015-0917-9.
[8] Reingold A. Outbreak investigations – a perspective. Emerg Infect Dis 1998;4:21–7. https://doi.org/10.3201/eid0401.980104.
[9] Haut Conseil de la Santé Publique. Actualisation des recommandations relatives aux Bactéries Hautement Résistantes aux antibiotiques émergentes (BHRe). 2019. Available at: https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=758 [last accessed March 2021].
[10] European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints – breakpoints and guidance. 2021. Available at: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf [last accessed March 2021].
[11] Jousset AB, Dabos L, Bonnin RA, Girlich D, Potron A, Cabanel N, et al. CTX-M-15-producing *Shewanella* species clinical isolate expressing OXA-535, a chromosome-encoded OXA-48 variant, putative progenitor of the plasmid-encoded OXA-436. Antimicrob Agents Chemother 2017;62. https://doi.org/10.1128/AAC.01879-17. e01879-17.
[12] Moyoshi-Akiyama T, Hayakawa K, Ohmagari N, Shimojima M, Kirikae T. Multilocus sequence typing (MLST) for characterization of *Enterobacter cloacae*. PLoS One 2013;8:e66358. https://doi.org/10.1371/journal.pone.0066358.
[13] Vogt S, Löffler K, Dinkelacker AG, Bader B, Autenrieth IB, Peter S, et al. Fourier-Transform Infrared (FTIR) spectroscopy for typing of clinical *Enterobacter cloacae* complex isolates. Front Microbiol 2019;10:2582. https://doi.org/10.3389/fmicb.2019.02582.
[14] Rakovitsky N, Frenk S, Kon H, Schwartz D, Temkin E, Solter E, et al. Fourier Transform Infrared spectroscopy is a new option for outbreak investigation: a retrospective analysis of an extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* outbreak in a neonatal intensive care unit. J Clin Microbiol 2020;58. https://doi.org/10.1128/JCM.00098-20. e00098-20.
[15] Martak D, Valot B, Sauget M, Cholley P, Thouverez M, Bertrand X, et al. Fourier-Transform InfraRed spectroscopy can quickly type Gram-negative bacilli responsible for hospital outbreaks. Front Microbiol 2019;10:1440. https://doi.org/10.3389/fmicb.2019.01440.
[16] Wendel Garcia PD, Fumeaux T, Guerci P, Heuberger DM, Montomoli J, Roche-Campo F, et al. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: initial report of the international RISC-19-ICU prospective observational cohort. EClin Med 2020;25:100449. https://doi.org/10.1016/j.eclinm.2020.100449.
[17] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.
[18] Hoxha A, Kärki T, Giambi C, Montano C, Sisto A, Bella A, et al. Attributable mortality of carbapenem-resistant *Klebsiella pneumoniae* infections in a prospective matched cohort study in Italy, 2012–2013. J Hosp Infect 2016;92:61–6. https://doi.org/10.1016/j.jhin.2015.06.018.
[19] Gomez-Simmonds A, Annavajhala MK, McConville TH, Dietz DE, Shoucri SM, Laracy JC, et al. Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital. J Antimicrob Chemother 2021;76:380–4. https://doi.org/10.1093/jac/dkaa466.
[20] Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, et al. Hospital-acquired infections in critically ill patients with COVID-19. Chest 2021;160:454–65. https://doi.org/10.1016/j.chest.2021.04.002.
[21] Tan X, Kim HS, Baugh K, Huang Y, Kadiyala N, Wences M, et al. Therapeutic options for metallo-β-lactamase-producing Enterobacterales. Infect Drug Resist 2021;14:125–42. https://doi.org/10.2147/idr.s246174.
[22] Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR. Infections caused by carbapenem-resistant Enterobacteriaceae: an update on therapeutic options. Front Microbiol 2019;10:80. https://doi.org/10.3389/fmicb.2019.00080.
[23] Giacobbe DR, Ciacco E, Girmenia C, Pea F, Rossolini GM, Sotgiu G, et al. Evaluating cefiderocol in the treatment of multidrug-resistant Gram-negative bacilli: a review of the emerging data. Infect Drug Resist 2020;13:4697–711. https://doi.org/10.2147/IDR.S205309.
[24] Izdebski R, Baraniak A, Herda M, Fiett J, Bonten MJ, Carmeli Y, et al. MLST reveals potentially high-risk international clones of *Enterobacter cloacae*. J Antimicrob Chemother 2015;70:48–56. https://doi.org/10.1093/jac/dku359.
[25] Gomez-Simmonds A, Annavajhala MK, Wang Z, Macesic N, Hu Y, Giddins MJ, et al. Genomic and geographic context for the evolution of high-risk carbapenem-resistant *Enterobacter cloacae* complex clones ST171 and ST78. mBio 2018;9. https://doi.org/10.1128/mBio.00542-18. e00542-18.
[26] Harada S, Aoki K, Ohkushi D, Okamoto K, Takehana K, Akatsuchi T, et al. Institutional outbreak involving multiple clades of IMP-producing *Enterobacter cloacae* complex sequence type 78 at a cancer center in Tokyo, Japan. BMC Infect Dis 2021;21:289. https://doi.org/10.1186/s12879-021-05952-9.
[27] Loveday HP, Lynam S, Singleton J, Wilson J. Clinical glove use: healthcare workers' actions and perceptions. J Hosp Infect 2014;86:110–16. https://doi.org/10.1016/j.jhin.2013.11.003.
[28] Ruis AR, Shaffer DW, Shirley DK, Safdar N. Teaching health care workers to adopt a systems perspective for improved control and prevention of health care-associated infections. Am J Infect Control 2016;44:1360–4. https://doi.org/10.1016/j.ajic.2016.04.211.
[29] Nakamura I, Fujita H, Tsukimori A, Kobayashi T, Sato A, Fukushima S, et al. Scenario-based simulation health care education for performance of hand hygiene. Am J Infect Control 2019;47:144–8. https://doi.org/10.1016/j.ajic.2018.07.024.
[30] Haute Autorité de Santé. Grille de recueil, consignes d'aide au remplissage et éléments de preuve 2019 – ICSHA3. 2019. Available at: https://www.has-sante.fr/upload/docs/application/pdf/2019-04/grille_de_recueil_icsha.3_2019.pdf [last accessed November 2021].
[31] Russotto V, Cortegiani A, Raineri SM, Giarratano A. Bacterial contamination of inanimate surfaces and equipment in the

intensive care unit. J Intensive Care 2015;3:54. https://doi.org/10.1186/s40560-015-0120-5.

[32] Smolders D, Hendricks B, Rogiers P, Mul M, Gordts B. Acetic acid as a decontamination method for ICU sink drains colonized by carbapenemase-producing Enterobacteriaceae and its effect on CPE infections. J Hosp Infect 2019;102:82—8. https://doi.org/10.1016/j.jhin.2018.12.009.

[33] Hofmaenner DA, Wendel Garcia PD, Duvnjak B, Chakrakodi B, Maier JD, Huber M, et al. Bacterial but no SARS-CoV-2 contamination after terminal disinfection of tertiary care intensive care units treating COVID-19 patients. Antimicrob Resist Infect Control 2021;10:11. https://doi.org/10.1186/s13756-021-00885-z.

[34] de Man TJB, Yaffee AQ, Zhu W, Batra D, Alyanak E, Rowe LA, et al. Multispecies outbreak of Verona Integron-encoded Metallo-β-lactamase-producing multidrug resistant bacteria driven by a promiscuous incompatibility group A/C2 plasmid. Clin Infect Dis 2021;72:414—20. https://doi.org/10.1093/cid/ciaa049.

[35] Büchler AC, Wüthrich D, Jauslin MW, Egli A, Widmer AF. Nosocomial transmission of a BlaVIM-2 carbapenemase integron between isolates of two different *Pseudomonas* species. Infect Control Hosp Epidemiol 2021:1—3. https://doi.org/10.1017/ice.2021.39.

[36] Yamagishi T, Matsui M, Sekizuka T, Ito H, Fukusumi M, Uehira T, et al. A prolonged multispecies outbreak of IMP-6 carbapenemase-producing Enterobacterales due to horizontal transmission of the IncN plasmid. Sci Rep 2020;10:4139. https://doi.org/10.1038/s41598-020-60659-2.

[37] Stjarne Aspelund A, Sjostrom K, Olsson Liljequist B, Morgelin M, Melander E, Pahlman LI. Acetic acid as a decontamination method for sink drains in a nosocomial outbreak of metallo-betalactamase-producing *Pseudomonas aeruginosa*. J Hosp Infect 2016;94:13—20. https://doi.org/10.1016/j.jhin.2016.05.009.

[38] Falagas ME, Thomaidis PC, Kotsantis IK, Sgouros K, Samonis G, Karageorgopoulos DE. Airborne hydrogen peroxide for disinfection of the hospital environment and infection control: a systematic review. J Hosp Infect 2011;78:171—7. https://doi.org/10.1016/j.jhin.2010.12.006.

[39] Passaretti CL, Otter JA, Reich NG, Myers J, Shepard J, Ross T, et al. An evaluation of environmental decontamination with hydrogen peroxide vapor for reducing the risk of patient acquisition of multidrug-resistant organisms. Clin Infect Dis 2013;56:27—35. https://doi.org/10.1093/cid/cis839.

[40] Liu H, Fei CN, Zhang Y, Liu GW, Liu J, Dong J. Presence, distribution and molecular epidemiology of multi-drug-resistant Gram-negative bacilli from medical personnel of intensive care units in Tianjin, China, 2007—2015. J Hosp Infect 2017;96:101—10. https://doi.org/10.1016/j.jhin.2017.01.012.

[41] Fernandez-Verdugo A, Forcelledo L, Rodríguez-Lozano J, Rodríguez-Lucas C, Barreiro-Hurlé L, Canut A, et al. Prospective multicentre study of rectal carriage of multidrug-resistant Enterobacteriaceae among health-care workers in Spain. Clin Microb Infect 2020;26:649.e1—4. https://doi.org/10.1016/j.cmi.2020.01.015.

[42] Bitterman R, Geffen Y, Rabino G, Eluk O, Warman S, Greenblatt AS, et al. Rate of colonization of health care workers by carbapenem-resistant Enterobacteriaceae in an endemic hospital: a prospective study. Am J Infect Control 2016;44:1053—4. https://doi.org/10.1016/j.ajic.2016.02.027.