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Spread of OXA-48-producing *Klebsiella pneumoniae* among COVID-19-infected patients: The storm after the storm

Isidro García-Meniño[a,b], Lorena Forcelledo[c,d], Yaiza Rosete[e], Emilio García-Prieto[c,f], Dolores Escudero[c,d], Javier Fernández[d,e,g,*]

[a] *Laboratorio de Referencia de Escherichia Coli (LREC), Departamento de Microbiología y Parasitología, Facultad de Veterinaria, Universidad de Santiago de Compostela (USC), Lugo, Spain*
[b] *Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago, Spain*
[c] *Servicio de Medicina Intensiva, Hospital Universitario Central de Asturias, Oviedo, Spain*
[d] *Grupo de Microbiología Traslacional, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Spain*
[e] *Servicio de Microbiología, Hospital Universitario Central de Asturias, Oviedo, Spain*
[f] *Grupo de Investigación Traslacional en el Paciente Crítico, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain*
[g] *Research & Innovation, Artificial Intelligence and Statistical Department, iAST™, Oviedo, Spain*

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ABSTRACT

The impact of secondary infections by multidrug-resistant bacteria in COVID-19- infected patients has yet to be evaluated. Here, we report the clinical and molecular features of an outbreak of seven patients carrying CTX-M-15- and OXA-48-producing *Klebsiella pneumoniae* belonging to ST326 during COVID-19 pandemic in an ICU in northern Spain. Those patients were admitted to beds close to each other, two of them developed ventilator-associated pneumonia (VAP), one exhibited primary bacteremia and the remaining four were considered to be colonized. None of them was colonized prior to admission to the ICU an all, except one of those who developed VAP, were discharged. Hydroxychloroquine and lopinavir/ritonavir were administered to all of them as COVID-19 therapy and additionally, three of them received tocilizumab and corticosteroids, respectively. Reusing of personal protective equipment due to its initial shortage, relaxation in infection control measures and negative-pressure air in ICU rooms recommended for the protection of health care workers (HCWs), could have contributed to this outbreak. Maximization of infection control measures is essential to avoid secondary infections by MDR bacteria in COVID-infected patients.

Introduction

Health systems worldwide are confronted by COVID-19, one of the most serious challenges in modern medicine. The most complex struggle is happening in intensive care units (ICUs), where the use of personal protective equipment (PPE) including respiratory protection, long-sleeved water-resistant gown, eye protection (goggles or face shield), and gloves is considered essential for health care workers (HCWs) and is now widespread [1,2]. However, PPE shortages means items are commonly being reused on the same working day when HCWs move from one patient to another. This issue, together with other aspects such as i) the huge overload of work, that may result in a certain relaxation of infection control measures, ii) the hiring of unqualified personnel in ICUs, and iii) the impaired immune system of patients infected with COVID-19, could cause an increase in outbreaks of multidrug-resistant (MDR) bacteria among such patients in ICUs.

Case presentation

Our hospital (Hospital Universitario Central de Asturias, northern Spain), and specifically the ICU, was recently battling the COVID-19 pandemic. Since admitting the first patient to the ICU on February 29th, a total of 62 patients have passed through the unit. In recent weeks, seven ICU patients with clinical and/or surveillance samples that have tested positive for carbapenem-resistant *Klebsiella pneumoniae* have been detected (see source of colonization/infection and clinical data in Table 1). Bacterial identification was performed by MALDI TOF/MS (Bruker Daltonics,

* Corresponding author at: Servicio de Microbiología, Hospital Universitario Central de Asturias, Ave Roma s.n., 33011 Oviedo, Spain.
E-mail address: javifdom@gmail.com (J. Fernández).

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Table 1
Clinical features of COVID-19 patients colonized/infected by OXA-48 producing *Klebsiella pneumoniae*.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex/Age	Male/66	Male/67	Male/76	Male/69	Female/71	Male/54	Male/66
Comorbidities	None	Diabetes, Ischemic heart disease	Hypertension, Diabetes, Asthma, Epilepsy	None	Hypertension	SDRA-Influenza H1N1	Dilated cardiopathy, Schizophrenia
Type of interaction	Infection	Colonization	Infection	Infection	Colonization	Colonization	Colonization
Sample	Blood	Traqueal aspirate	Traqueal aspirate	Traqueal aspirate	Rectal swab	Rectal swab	Rectal swab
Type of infection	Primary bacteremia		VAP	VAP			
Prior Colonization	No	No	No	No	No	No	No
Days on general ward prior to ICU admission	1	4	0	3	0	0	0
Days from ICU admission to positive culture	9	9	9	4	7	15	12
Mechanical ventilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Previous antibiotics	Ceftriaxone, Azithromycin	Ceftriaxone, Pipera-cilin/Tazobactam	Ceftriaxone, Azithromycin, Pipera-cilin/Tazobactam, Vancomycin	Ceftriaxone, Azithromycin	Ceftriaxone	Ceftriaxone, Pipera-cilin/Tazobactam, Ceftazidime	Ceftriaxone, Ceftazidime, Meropenem
COVID treatment	HCQ, L/T, Corticoids	HCQ, L/T, Tocilizumab	HCQ, L/T, Corticoids, Tocilizumab	HCQ, L/T, Tocilizumab	HCQ, L/T	HCQ, L/T, Corticoids	HCQ, L/T
Outcome	Discharged	Discharged	Dead	Discharged	Discharged	Discharged	Discharged

ICU, intensive care unit; VAP, ventilator associated pneumonia; L/R, lopinavir/ritonavir; HCQ, hydroxychloroquine.

Bremen, Germany) and antimicrobial susceptibility testing carried out by the Microscan System (Beckman Coulter, Brea, CA, USA), and the results interpreted according to EUCAST (www.eucast.org). Bacterial DNA was extracted by boiling lysis method and extended-spectrum β-lactamase (ESBL) and carbapenemase encoding genes were screened by the AMR Flow Chip system (Máster Diagnóstica, Granada, Spain), conventional PCR and further sequencing as previously described [3], and all were positive for the $bla_{\text{CTX-M-15}}$ and $bla_{\text{OXA-48}}$ genes. Pulsed-field gel electrophoresis (PFGE) was carried out as described elsewhere using endonuclease XbaI and similarities evaluation was performed by the Dice coefficient using MVSP (Multivariate Statics Package for PCs, RockWare Inc.) [3], showing two similar pulsotypes (Supplementary Fig. 1) with a coefficient of similarity higher than 0.85 suggesting that all isolates were the same clone. Multilocus sequence typing (MLST) performed according to Pasteur guidelines (https://pubmlst.org/) revealed that isolates belonged to sequence type (ST) 326 (*gapA* 1, *infB* 1, *mdh* 1, *pgi* 1, *phoE* 1, *rpoB* 1, *tonB* 64) a clone previously related to OXA-48 dissemination in Spain [3,4].

Discussion

Since all patients were admitted to beds close to each other, and the relationship between their isolates was clonal (almost equal PFGE profiles with Dice similarities higher than 0.85), cross-transmission through the contaminated PPE of HCWs could be the main hypothesis of likely spread, considering that transmission via contaminated gowns and gloves has been described to be important in the nosocomial spread of *K. pneumoniae* strains [5]. It is of note that none of the patients were previously colonized by OXA-48-producing *Enterobacteriaceae*. Some factors that could have facilitated this outbreak are HCWs using the same PPE when attending to different patients in the same unit, or applying hydroalcoholic solution on top of their gloves and not directly on their skin as double-gloving was common, with only the outer gloves being changed between patients. At the beginning of the outbreak, following the identification of the first four patients, the use of a disposable gown over the PPE was implemented in the ICU, although another three patients were identified in the following 10 days. It is important to remember that PPE is designed for self-protection but does not avoid the transmission of germs between patients, while it could create a false sense of security in the wearer, leading to the neglect of other infection control measures. Also, and as a second hypothesis of transmission, the negative-pressure air recommended for the protection of HCWs during the COVID-19 outbreak (in contrast to the normally recommended positive pressure in ICUs) [2,6], could leave patients unprotected and play a role in the dissemination of MDR bacteria within ICUs.

The consequences of colonization/infection by multidrug-resistant (MDR) bacteria have not yet been evaluated in patients affected by COVID-19, but could be troubling for several reasons. First, the previously mentioned immune system dysfunction in these patients due to the disease itself and to the immunomodulatory therapeutic approach taken; and second, because of factors such as their often advanced age, comorbidities, long hospital stays and the numerous invasive procedures they are subjected to, all of which are risk factors in relation to colonization/infection by MDR-bacteria [5]. Already some studies have described that patients hospitalized with COVID-19 have acquired dangerous secondary bacterial infections, which appear strongly linked to death, (up to 50% of the total number of fatalities having such infections) [7,8]. In other viral pandemics scenarios, such as the 1918–1919 influenza pandemic, is hypothesized that most of the deaths were caused by secondary bacterial infections [9]. In those days, medicine was in the pre-antibiotic era, but nowadays the high pressure of MDR bacteria in some environments like ICUs, could also bring on serious problems during the COVID-19 pandemic.

Diagnosis of secondary MDR bacterial infections is tricky since they could be masked by alterations in acute infection markers caused by COVID-19 itself. Furthermore, it is important to distinguish between colonization and infection especially in non-sterile samples, while at the same time noting that when these bacteria are detected in sterile fluids such as blood cultures, it may be too late for optimal treatment to be implemented. In our series, two

patients developed ventilator-associated pneumonia, one exhibited primary bacteremia and the remaining four were considered to be colonized (Table 1). The three infected patients were treated with meropenem (MICs to this antibiotic were of 1 mg/L), but in two patients treatment had to be escalated to ceftazidime/avibactam due to an increase in meropenem MIC (32 mg/L) during therapy. All except one of those who developed VAP, was successfully discharged from ICU (Table 1).

Only a few antimicrobials are available for the treatment of infections caused by MDR bacteria in general and particularly for carbapenemase-producing *Enterobacteriaceae* [10]. In COVID-19-affected patients this situation is aggravated by factors such as organ disruption (renal and liver impairment) and potential interactions with immunomodulators or other drugs used in their treatment (antiretrovirals, macrolides, hydroxychloroquine, etc.). As such, new drugs such as new ß-lactams and ß-lactamase inhibitors (ceftazidime/avibactam, ceftolozane/tazobactam, ceftaroline…) could play an important role in the treatment of secondary infections caused by MDR bacteria in these patients.

Conclusion

There is still much to learn about the role and prevention of secondary infections by MDR bacteria and specifically carbapenemase-producing *Enterobacteriaceae* in patients affected by COVID-19. The maximization of infection control measures is essential, and more studies are needed to provide scientific evidence in this respect and to optimize their diagnosis and treatment in order to avoid the storm after the storm.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2020.11.001.

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