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Interhospital outbreak of *Burkholderia cepacia* complex ventilator-associated pneumonia (VAP) caused by contaminated mouthwash in coronavirus disease 2019 (COVID-19) patients

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To the Editor—In the global coronavirus disease 2019 (COVID-19) pandemic, up to 80% of the patients in intensive-care units (ICUs) have required invasive mechanical ventilation (IMV).[1] Inpatients receiving endotracheal intubation and IMV have increased risk of ventilator-associated pneumonia (VAP).[1,2]

Oral hygiene with chlorhexidine-based mouthwash is an important prevention measure for VAP[3]; however, outbreaks of *Burkholderia cepacia* complex associated with these products have been reported.[4,5] To our knowledge, this is the first report of a VAP outbreak caused by *B. cepacia* complex in COVID-19 patients admitted in ICUs involving 2 hospitals.

In November and December 2020, in a tertiary-care university hospital (hospital 1) in southern Brazil, 7 patients in a COVID-19 ICU and 3 patients in an adult ICU had positive cultures for *B. cepacia* complex (>10^6 CFU/mL) from endotracheal aspirate (ETA). During this period, 6 other patients in a mixed ICU in a private hospital (hospital 2) in the same region showed *B. cepacia* complex–positive cultures (Fig. 1).

As part of the intervention, contact-isolation precautions were implemented for all patients with *B. cepacia* complex–positive cultures. Microbiological data were reviewed to track the source of this contamination, and as reported previously, hospital 1 had experienced consecutive outbreaks of *B. cepacia* complex as a result of the use of intrinsically contaminated mouthwash, so this source was investigated first.[6]

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Burkholderia cepacia complex isolates recovered from ETA and mouthwashes at hospital 1 were characterized phenotypically using the BD-Phoenix automated system (Becton-Dickinson, Franklin Lakes, NJ). Hospital 2 used the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) system (Bruker Daltonics GmbH, Leipzig, Germany). All isolates (hospitals 1 and 2) were typed using the enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR) technique.[7] BioNumerics 6.5 software (Applied Maths, Sint-Martens-Latem, Belgium) was used to analyze band patterns.

In total, 16 patients had *B. cepacia* complex–positive cultures recovered from ETA; 12 (75%) these patients were hospitalized with COVID-19 (positive RT-PCR for severe acute respiratory coronavirus virus 2 [SARS-CoV-2]) (Fig. 1). The mean age of these patients was 66 years, and 69% were male. All patients received IMV from the first day of ICU admission. The median time between the beginning of IMV and the first isolation of *B. cepacia* complex was 14 days (interquartile range [IQR], 9–16).

Burkholderia cepacia complex was recovered (>2.7×10^5 CFU/mL) in unopened mouthwash bottles containing 0.12% chlorhexidine used in both hospital 1 (batch C9252, 250 mL) and hospital 2 (batch C9275, 1000 mL), all from the same company. This company's mouthwashes had been used at hospital 1 since January 2020 without isolation of *B. cepacia* complex in infections.

All isolates evaluated showed 100% genetic similarity, characterizing a monoclonal outbreak involving 3 ICUs and 2 hospitals caused by *B. cepacia* (confirmed by MALDI-TOF MS).

The manufacturer of these contaminated batches was implicated in a previous *B. cepacia* complex outbreak at hospital 1, 4 years prior (data reported by our research group).[6] In the

			Patient	Age - years	Gender	Reason for ICU admission	Bcc collection date	Sample	IMV- Bcc detection[a]	ICU Outcome	ERIC profile
HOSPITAL I	Mouthwash - batch 9252	COVID-19 ICU	1	74	Male	COVID-19	20-Nov-20	ETA	8	Death	A
			2	35	Male	COVID-19	9-Dec-20	ETA	9	Discharge	A
			3	62	Male	COVID-19	11-Dec-20	ETA	16	Death	A
			4	76	Male	COVID-19	11-Dec-20	ETA	10	Death	A
							27-Dec-20	ETA, Blood			A
			5	89	Female	COVID-19	15-Dec-20	ETA	16	Death	A
			6	69	Female	COVID-19	21-Dec-20	ETA	14	Discharge	A
			7	70	Female	COVID-19	28-Dec-20	ETA	22	Discharge	A
		Adult ICU	1	56	Male	IGS	4-Dec-20	ETA, Blood	24	Discharge	A
			2	30	Male	Drugs, after CA	7-Dec-20	ETA	9	Discharge	A
			3	44	Male	Seizure, ARpI	15-Dec-20	ETA	12	Discharge	A
			Commercial mouthwash				11-Dec-20	Unopened bottle			A
HOSPITAL II	Mouthwash - batch 9275	Mixed ICU[b]	1	68	Male	COVID-19	23-Nov-20	ETA	13	Death	A
			2	72	Female	COVID-19	3-Dec-20	ETA, Blood	8	Death	A
			3	77	Male	IGS	6-Dec-20	ETA, Blood	15	Death	A
			4	58	Male	COVID-19	16-Dec-20	ETA	16	Death	A
			5	79	Male	COVID-19	10-Dec-20	ETA	11	Death	A
			6	63	Female	COVID-19	8-Dec-20	ETA, Blood	16	Death	A
			Commercial mouthwash				9-Dec-20	Unopened bottle			A

Fig. 1. Schematic description of *B. cepacia* complex isolates recovered from mechanically ventilated patients and unopened mouthwash bottles in an intra- and interhospital outbreak. (a) Time (in days) between the beginning of invasive mechanical ventilation (IMV) and *B. cepacia* complex detection (collection of clinical sample). (b) Patients with and without COVID-19 are admitted to the mixed ICU. Note. ICU, intensive care unit; IGS, Instability after gastrointestinal surgery; CA, cardiac arrest; ARpI, acute respiratory insufficiency; ETA, endotracheal aspirate; ERIC, Enterobacterial repetitive intergenic consensus polymerase chain reaction.

current outbreak, the hospitals notified again the National Health Surveillance Agency (ANVISA) and the manufacturer. More effectively, a voluntary national recall on December 16, 2020, by the manufacturer resulted in removal of all affected batches. According to the FDA, a likely source of *B. cepacia* complex contamination in aqueous products appears to be contaminated water used in manufacturing.[4] The presence of *B. cepacia* complex in unopened bottles from different batches of mouthwash strongly suggests contamination during the manufacturing process, and as with *B. lata* in a study conducted by Leong et al[8], our findings also suggest contamination during manufacturing.

Nosocomial cross transmission between patients with *B. cepacia* complex appears unlikely in this case. In hospital 1, the facilities and staff are not shared between the ICUs, and the adult ICU has single-bed rooms and the COVID-19 ICU 2-bed rooms. In hospital 2, inpatients with COVID-19 are single-bed rooms.

Of the total of 12 patients with VAP by *B. cepacia* complex and with COVID-19, 9 (75%) died. Of the 4 patients with VAP by *B. cepacia* complex and without COVID-19, only 1 (25%) died (Fig. 1). The time of IVM of these patients (without COVID-19) was 54.8% shorter than the patients with *B. cepacia* complex and SARS-CoV-2 coinfection. The median times of IVM were 31 for patients with COVID-19 and 17 days for patients without COVID-19. These results suggest that coinfection with SARS-CoV-2 and *B. cepacia* complex may increase the time of IMV, similarly to the case reported by Osman and Nguyen.[9]

Another observation here was the high number of deaths, although attributable mortality was not calculated. Although data on coinfection between SARS-CoV-2, fungi or bacteria, including *B. cepacia* complex, were reported,[10] data on the time of IMV and mortality attributed to these patients are still little explored and require further investigation.

Outbreaks of *B. cepacia* complex PAV caused by intrinsically contaminated chlorhexidine-based mouthwashes have been well reported.[4-6] The ability of *B. cepacia* complex to remain viable in chlorhexidine appears to result from a combination of efflux pump activity, biofilm formation, and cell-wall impermeability.[8] These factors in themselves are extremely important because these products are used for critically ill patients. However, in the context of the COVID-19 pandemic, an outbreak appears to have even more serious consequences. The few cases reported in hospital 2 showed that VAP occurred in a short period, with a high incidence (50%) of bacteremia secondary to VAP and 100% mortality of affected patients.

In conclusion, effective surveillance with practical monitoring by a multidisciplinary team and rapid implementation of outbreak control are even more necessary in mixed ICUs and COVID-19 ICUs. We strongly suggest that national regulatory authorities establish protocols for the detection of *B. cepacia* complex in

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chlorhexidine-based products, ensuring microbiological quality of the finished product in addition to patient safety, so that similar outbreaks can be prevented.

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A practical approach to defining aerosol-generating procedures

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To the Editor—The use of appropriate personal protective equipment (PPE) is crucial in preventing transmission of SARS-CoV-2 to healthcare workers (HCWs) when caring for COVID-19 patients. However, the debate on the importance of different modes of transmission of SARS-CoV-2 continues, and it affects the type of PPE recommended for use.[1] Moreover, with this pandemic still in progress, the issue of conserving PPE is a practical dilemma.[2] Clinicians are naturally concerned if they are asked to undertake a procedure potentially generating aerosols while using droplet precautions. Countries and specialist societies define and specify the list of aerosol-generating procedures (AGPs) differently. In practical terms, a risk assessment is needed for some procedures with borderline risk such as nasogastric tube insertion. Although the recommendations of PPE for known or suspect COVID cases is clearer, there is greater uncertainty regarding precautions for nonsuspect cases, especially in high-prevalence settings.

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The Singapore National Infection Prevention and Control Committee developed a list of "Procedures of Concern" (Table 1) to help HCWs identify procedures of higher risk that require additional measures to prevent transmission from unidentified COVID-19 cases in the hospital for other reasons. The risk is dependent on the procedure, community prevalence of COVID-19, proportion of diagnosed and isolated infections, and healthcare facility–level screening.

Procedures of concern are defined as any medical procedure that can induce the production of aerosols of various sizes, including small (<5 μm) particles containing SARS-CoV-2. For all other procedures, standard precautions should apply. During periods of low community prevalence, the emphasis should be on the use of standard precautions.[3] In general, AGPs and procedures of concern should be avoided in patients with suspected or confirmed cases of COVID-19, unless urgently required. Ideally, these should be performed in an airborne infection isolation room (AIIR) whenever possible.[4] When unavailable and the procedure must occur in situ (eg, intubation during resuscitation), staff are advised to draw the privacy curtains and remove any shared equipment, supplies, or linen from the immediate vicinity prior to performing the AGP. In addition, the number of HCWs who are