


## Letter to the Editor

# 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).<sup>1</sup> Inpatients receiving endotracheal intubation and IMV have increased risk of ventilator-associated pneumonia (VAP).<sup>1,2</sup>

Oral hygiene with chlorhexidine-based mouthwash is an important prevention measure for VAP<sup>3</sup>; however, outbreaks of *Burkholderia cepacia* complex associated with these products have been reported.<sup>4,5</sup> 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<sup>6</sup> 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.<sup>6</sup>

*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.<sup>7</sup> BioNumerics 6.5 software (Applied Maths, Sint-Martens-Latem, Belgium) was used to analyze band patterns.

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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<sup>5</sup> 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).<sup>6</sup> In the 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.<sup>4</sup> 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.<sup>8</sup>, 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

		Patient	Age - years	Gender	Reason for ICU admission	Bcc collection date	Sample	IMV- Bcc detection <sup>a</sup>	ICU Outcome	ERIC profile	
HOSPITAL I	Mouthwash - batch 9252	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		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.

(Fig. 1). The time of IMV 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 IMV 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.<sup>9</sup>

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,<sup>10</sup> 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.<sup>4-6</sup> 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.<sup>8</sup> 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 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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