Infection Control & Hospital Epidemiology (2024), **45**, 677–680
doi:10.1017/ice.2023.241

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Concise Communication

Diving deep for the needle in the haystack: An outbreak investigation of *Burkholderia cenocepacia* bacteremia

Abdul Ghafur MRCP[1], Praveen Balaguru MD[1], S. G. Ramanan DM[2], Rejiv Rajendranath DM[2], Revathi Raj MRCP[3], Mohammed Zehran MRCP[2], T. Raja DM[2], Jose M. Easow AB[2], Sankar Srinivasan AB[2], Dedeepiya Devaprasad MD[4], Thilakavathy Sukumar MBBS[5], Praveen Nilgar MS[5], K. Sakthivel BPharm[6], Rakkesh M. Nirumal MD[6], K. Chandra MSc[7], Sree V. Lakshmi MD[8], Nandini Sethuraman MD[9], Yamuna Devi Bakthavatchalam PhD[10] and Balaji Veeraraghavan MD[10]

[1]Infectious Diseases, Apollo Cancer Institute, Teynampet, Chennai, [2]Medical Oncology, Apollo Cancer Institute, Teynampet, Chennai, [3]Pediatric Hemato-Oncology, Apollo Cancer Institute, Teynampet, Chennai, [4]Critical Care, Apollo Cancer Institute, Teynampet, Chennai, [5]Apollo Cancer Institute, Teynampet, Chennai, [6]Pharmacy, Apollo Cancer Institute, Teynampet, Chennai, [7]Infection Control, Apollo Cancer Institute, Teynampet, Chennai, [8]Microbiology, Apollo Cancer Institute, Teynampet, Chennai, [9]Microbiology, Apollo Hospitals, Greams Road, Chennai and [10]Microbiology, Christian Medical College, Vellore

Abstract

In an Indian oncology setting, between August and December 2021, 56 patients, developed *Burkholderia cenocepacia* bacteremia. An investigation revealed a contaminated batch of the antiemetic drug palonosetron. The outbreak was terminated by withdrawing the culprit batch and the findings were reported promptly to regulatory authorities.

(Received 21 April 2023; accepted 10 October 2023; electronically published 4 January 2024)

Burkholderia cepacia complex is a group of environmental bacteria which can cause nosocomial outbreaks. It is a complex of >20 species, including *B. cenocepacia*. Here, we report our investigation into an outbreak of *B. cenocepacia* bacteremia in an oncology hospital.

Methods

Apollo Cancer Institute is a 300-bed hospital that predominantly provides oncology care and belongs to a group of hospitals. Blood cultures were incubated in BacT/ALERT bottles (Biomerieux, Marcy-l'Étoile, France) and identification was done by VITEK 2 compact analyzer (Biomerieux). We cultured 50 environmental samples, 24 intravenous fluid samples, 24 medications, and 12 refrigerated and reconstituted antibiotic preparations.[1] We collected surveillance blood cultures from all inpatients and outpatients with central lines or ports who had received cancer chemotherapy. Drug samples were cultured in 2 hospitals simultaneously. In our hospital microbiological identification was done by VITEK 2 whereas in the other hospital of our group it was done by MALDI-TOF (VITEK MS, Biomerieux). For whole-genome sequencing (WGS), we sent isolates to the Christian Medical College, Vellore, where WGS was conducted on an Illumina HiSeq 2500 platform (Illumina, San Diego, CA). Sequence types were identified using the MLST finder (https://cge.food.dtu.dk/services/MLST/). Resistance genes were identified using AMRfinderplus (https://github.com/ncbi/amr).

Corresponding author: Abdul Ghafur; Email: drghafur@hotmail.com

Cite this article: Ghafur A, Balaguru P, Ramanan SG, *et al.* Diving deep for the needle in the haystack: An outbreak investigation of *Burkholderia cenocepacia* bacteremia. *Infect Control Hosp Epidemiol* 2024. 45: 677–680, doi: 10.1017/ice.2023.241

Between August 17 and December 24, 2021, 56 patients were identified with *B. cenocepacia* bacteremia (Fig. 1). The index patient in August 2021 was a child with chronic granulomatous disease who developed *B. cenocepacia* bacteremia while receiving treatment in an outside hospital and continued to grow *B. cenocepacia* from blood cultures upon transfer to our hospital. The isolate from the other hospital was resistant to ceftazidime, whereas the patient's subsequent *B. cenocepacia* isolate in our hospital as well as all *B. cenocepacia* isolates from patients in this outbreak were susceptible to ceftazidime.

All but 1 patient had central lines or chemotherapy ports and had recently received chemotherapy, spanning from 2 days to a few weeks prior to developing bacteremia.

Among environmental samples, the gel inside the sealed ice packs (used to transport reconstituted chemotherapy drugs from the mixing cabinet to the bedside) grew *B. cenocepacia*, but the isolates' antibiotic susceptibility pattern (antibiogram) was different. All ice packs were replaced with brand-new ones.

Another hospital in our group had reported an outbreak of *B. cepacia* bacteremia a few months earlier, in which the source was identified as ultrasound jelly.[2] We therefore cultured several opened and unopened bottles of ultrasound and electrocardiogram jelly. A few of these bottles grew *B. cenocepacia*, but these isolates also had a different antibiogram from the patient isolates in the current outbreak. Although all hospitals in our group had called back the entire stock of contaminated ultrasound jelly, we discovered that a few bottles were left behind in the cabinets at the end-user level and ensured a proper recall by taking the appropriate steps.

Chart review revealed that only oncology patients had *B. cenocepacia* infections and that patients belonging to only

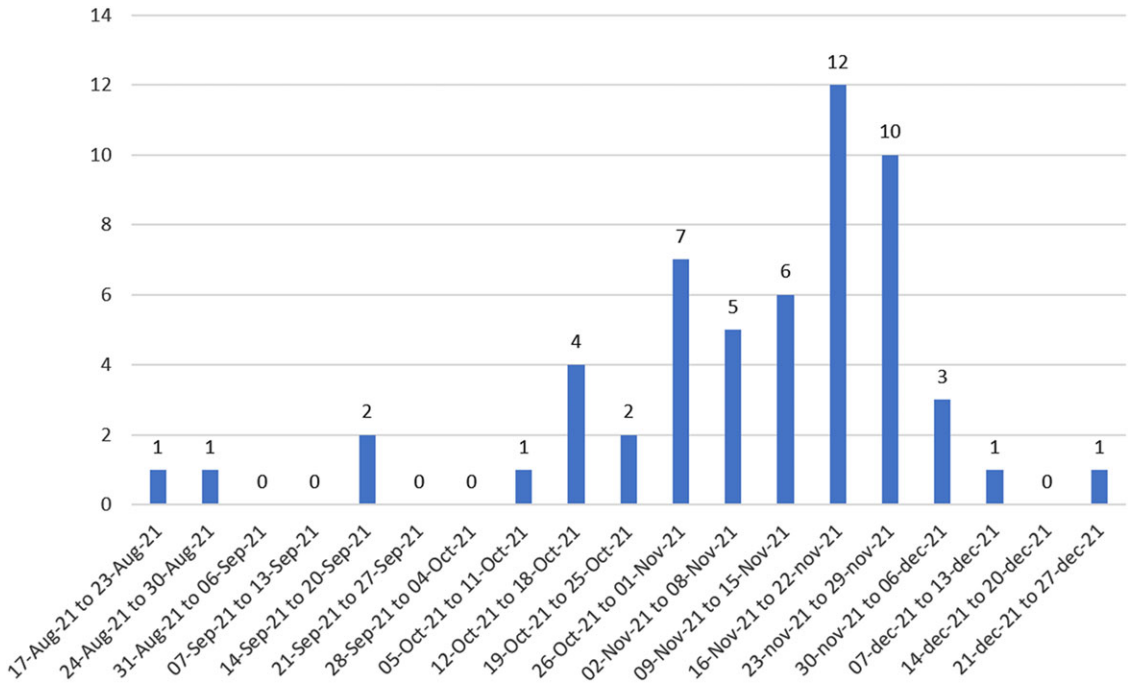

Figure 1. Weekly incidence of new cases.

certain oncologists had *B. cenocepacia* bacteremia. Analysis of the drug, fluid, and device utilization patterns of all the oncologists in the hospital established that 5 oncologists were using palonosetron as an antiemetic, while others, who had no infected patients, used ondansetron. We cultured several vials of palonosetron. Of the 5 vials of a particular brand of palonosetron, 4 grew *B. cenocepacia*. The antibiogram of all isolates was similar to the clinical isolates. Furthermore, 5 additional vials of palonsetron were cultured in a separate laboratory of another hospital in our group; 4 of these 5 vials grew *B. cenocepacia* with the same antibiogram. However, vials of palonosetron belonging to a different brand used in our hospital during the same period were culture negative. The culprit batch was manufactured in July 2021, coinciding with the onset of the outbreak in August 2021. The batch was immediately withdrawn from the pharmacy.

Moreover, 4 clinical isolates and 4 drug isolates were sent for WGS analysis. All 8 isolates of *B. cenocepacia* belonged to ST217. We examined the SNPs in their core genome. The SNP distance comparison matrix revealed differences in only 40 SNPs, suggesting a common origin and clonality. The SNP matrices in B1 and B3 were similar. A phylogenetic tree based on SNPs showed all 8 isolates belongs to 1 phylogenetic cluster, which indicates clonality demonstrating the epidemiological link (Fig. 2).

Follow-up after the source identification

All infected patients had received the culprit drug. We notified the Drugs Controller General of India (CDGI) and the drug manufacturer about the outbreak, requesting an immediate withdrawal of the culprit batch. DCGI withdrew the culprit batch with immediate effect. We tracked all the patients within our hospital system who had received the culprit drug, counselled them on the outbreak, and carried out surveillance cultures from their central lines, thus identifying one-third of the patients in the outbreak cohort. Central lines and ports were removed from all patients with positive cultures.

Discussion

Burkholderia cenocepacia outbreaks with documented sources include antiemetics like granisetron,[3] ultrasound jelly,[2,4,5] Ringer's Lactate solution,[6] chlorhexidine,[7,8] and octenidine mouthwash solution.[9] Our paper describes an outbreak investigation with several peculiarities, including false leads along the way.

The antibiograms of the isolate from the presumed index patient after admission to our hospital and those of the subsequent patients were similar. This pattern led us to believe that the patient was colonized with *B. cenocepacia* on admission and later had a clinical infection. We initially hypothesized that subsequent patients could have contracted the infection from the index patient due to a potential breach in the infection control measures. Hence, we concentrated on stepping up infection control measures to close any potential gap, including real-time video surveillance of adherence to hand hygiene and contact precautions and escalating environmental cleaning to the best possible level. However, when previously asymptomatic patients developed *B. cenocepacia* bacteremia within 48 hours of admission for chemotherapy, the epidemiology led us to evaluate further.

The growth of *B. cenocepacia* from icepacks used in the chemotherapy drug carry boxes was a red herring. The antibiogram of these isolates, though similar among isolates from various icepack gels, was entirely different from the clinical isolates. The growth of *B. cenocepacia* in the ultrasound jelly was another red herring.

Epidemiologic analyses of patients' physicians and drug exposures were the keys to identifying the source of this outbreak. WGS provided the resolution to confirm the relatedness of the *B. cenocepacia* strain isolated from the patients and the medication vials.

https://doi.org/10.1017/ice.2023.241 Published online by Cambridge University Press

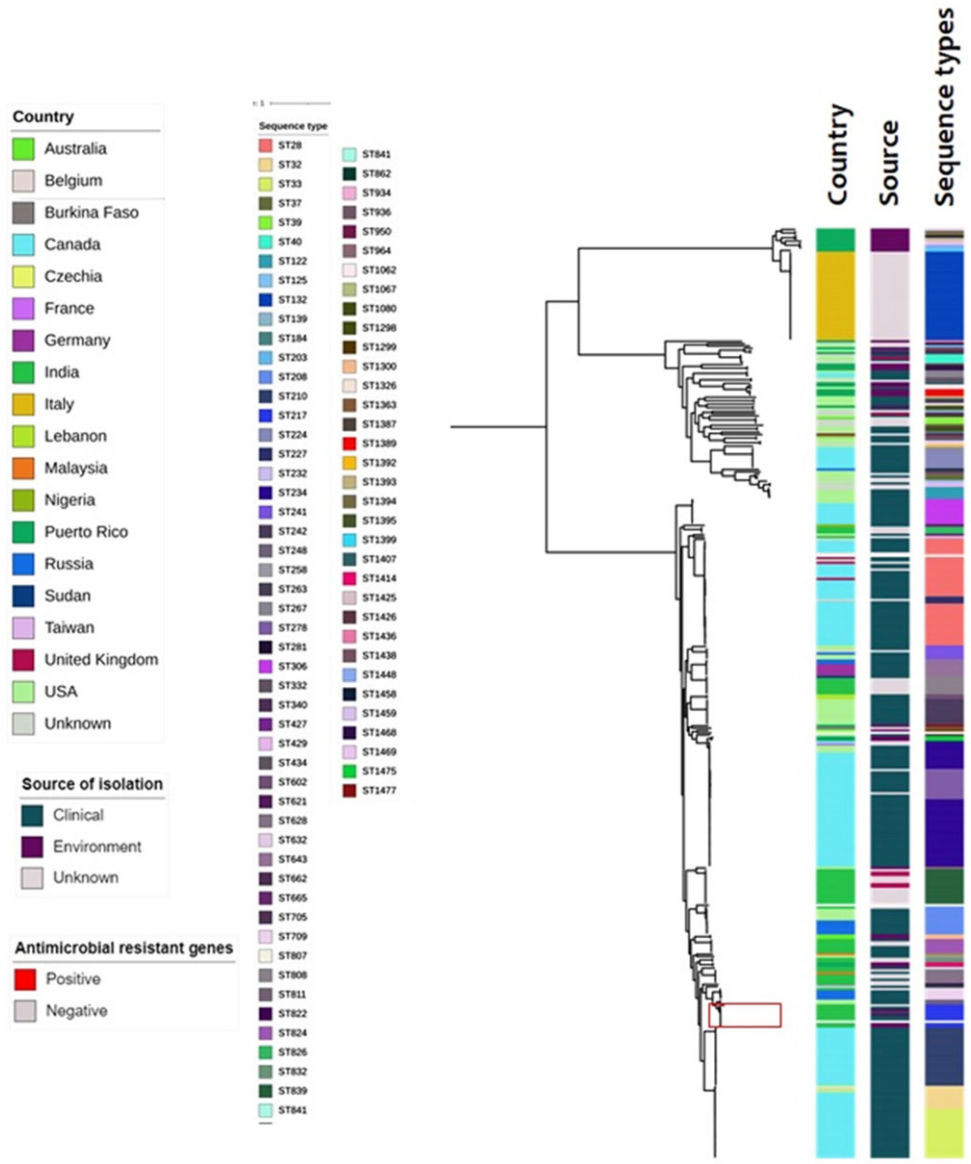

Figure 2. Maximum likelihood phylogenetic of *Burkholderia cepacia* complex. Outbreak isolates (marked as red box in phylogenetic tree) are very close to the Indian isolates that have been reported previously.

In conclusion, this outbreak of *B. cenocepacia* bacteremia was linked to a contaminated batch of palonosetron. Systematic evaluation and swift follow-up measures were needed to curtail the outbreak.

Acknowledgments.

Financial support. No financial support was provided relevant to this article.

Competing interests. All authors report no conflicts of interest relevant to this article.

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https://doi.org/10.1017/ice.2023.241 Published online by Cambridge University Press