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Review Article

Burkholderia cepacia complex nosocomial outbreaks in India: A scoping review

Ankita Saran[1], Amit Agarwal[2], Swapna Anandrao Mali[5], Lipika Singhal[3], Prabhu B. Patil[4] & Vikas Gautam[1]

Departments of [1]Medical Microbiology, & [2]Telemedicine, Postgraduate Institute of Medical Education and Research, [3]Department of Microbiology, Government Medical College and Hospital, [4]Department of Bacterial Genomics and Evolution Laboratory, CSIR-Institute of Microbial Technology, Chandigarh, & [5]Department of Microbiology, Topiwala National Medical College & BYL Nair Charitable Hospital, Mumbai, India

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Burkholderia cepacia **complex (Bcc) is an opportunistic pathogen that causes severe infections in immunocompromised individuals. It is a common contaminant of medical drugs, solutions and devices used in healthcare setups. This scoping review aimed to assess Bcc outbreaks in Indian hospital settings and address a wide range of sources to improve outbreak management. As per PRISMA-ScR guidelines, electronic databases 'Embase', 'PubMed' and 'Web of Science' were searched from 1993 to September 2024 to identify studies reporting *Burkholderia cepacia* complex outbreaks across India. The search identified 22 outbreak reports meeting the inclusion criteria. Bacteremia was the most common presentation in twenty studies, followed by acute-onset post-operative endophthalmitis in two studies. In 14 outbreak studies, *B. cepacia* was the identified species, whereas five studies had Bcc; one study each had *B. cenocepacia*, *B. multivorans* and *B. contaminans* isolated. Most outbreaks were associated with contaminated pharmaceuticals (45.4%) and medical (18.1%) products in contrast to the environment as a source (13.6%). Multi-locus sequence typing (MLST) was employed to study clonality among isolates in six outbreaks. This review highlights that varied medical products and environmental surfaces/objects can harbour Bcc and act as potential sources of Bcc outbreaks in hospitals. Ensuring immediate identification of Bcc from clinical samples, regular sterility checks, thorough epidemiological investigations, and timely infection control and prevention measures are critical to help manage and prevent these outbreaks and the subsequent mortality.**

Key words *Burkholderia cepacia* complex - contaminated pharmaceutical products - India - MLST - molecular typing - outbreak

Members of the *Burkholderia cepacia* complex (Bcc) consisting of 22 species are oxidase-positive, rod-shaped, non-fermenting Gram-negative bacteria (NFGNB)[1,2]. They are found ubiquitously in various natural and man-made habitats owing to their exceptional metabolic adaptability[3]. These opportunistic pathogens are responsible for a wide range of infections and complications in immunocompromised individuals[4,5]. Their ability to cause life-threatening infections in intensive care settings and paediatric patients is well recognized.

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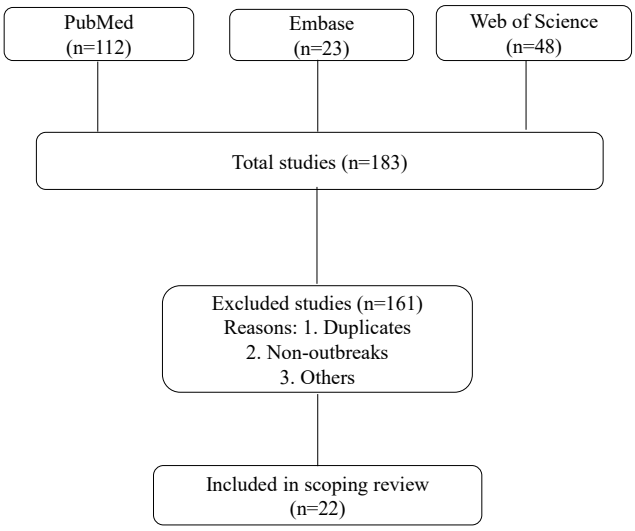

Figure. Flowchart outlining the review process for including the studies.

Bcc causes severe pulmonary infections in cystic fibrosis (CF) and chronic granulomatous disease (CGD) patients[6,7]. Additionally, it induces bacteremia in patients, with host and environmental risk factors like prolonged hospital stay, medical co-morbidities, use of central venous catheters (CVC) and exposure to medical products, like ultrasound gels and devices[8,9]. The bacteria's survival and replication in indwelling invasive devices, resistance to disinfectants, and ability to persist in moist environments and surfaces like water tanks, sinks, taps and others with restricted nutrition highlight its significance as an emerging nosocomial pathogen globally. Bcc's endurance to pharmaceutical products and devices makes them function as a potential reservoir of infection in hospital settings, facilitating outbreaks in the event of breaches in infection prevention and control practices (IPC)[3,5,10]. The patient-to-patient transmission also contributes to Bcc colonization. Bcc exhibits a distinctive antimicrobial profile, posing challenges to treatment. Intrinsic resistance, especially to antibiotics like polymyxins and aminoglycosides, and rising multi-drug resistance further complicates management[2,11]. Moreover, a limited understanding of pathogenicity, laboratory identification and differentiation from other NFGNBs leads to underreporting and inadequate treatment of Bcc infections.

Numerous Bcc outbreaks from hospital settings have been reported globally, including those from India. Bcc has been known to contaminate many medical products, such as ultrasound gel[12], detergents, and moisturizing creams[13], pharmaceutical preparations like IV fluids[14], chlorhexidine solutions and mouthwash[15], rubber stoppers of drug vials[16], nebulized salbutamol[17] and devices like respiratory equipment[17]. It is known to survive in distilled water by utilizing trace amounts of organic compounds and carbon dioxide as energy sources[18,19]. Intravenous (IV) medications, including antiemetic drug vials and multidose amikacin vials, have been identified as sources of infection. These outbreaks have been reported in ICU settings and dialysis units and are common among paediatric populations[16,20]. However, in the available literature, a comprehensive study analyzing the Bcc outbreaks, specifically of Indian origin, is lacking. To address this gap and create awareness, we conducted a scoping review on nosocomial Bcc outbreaks from India that were published in peer-reviewed scientific journals. The objective of the review was to analyze infection sources, outbreak investigations, affected patient populations, and control strategies in the Indian context.

Materials & Methods

The study followed PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines. The PRISMA-ScR 22 points checklist (Supplementary Table) has been referred to while formulating this review. Databases such as 'PubMed' (*https://pubmed.ncbi.nlm.nih.gov*), 'Embase' (*https://www.embase.com*) and 'Web of Science' (*https://clarivate.com*) were utilized. Literature published between 1993 and September 2024 and only in English was included in this review. Furthermore, the references cited in the included studies were assessed (Figure). The combination of search terms used was as follows: (*Burkholderia cepacia* complex OR *Burkholderia* species OR *Pseudomonas cepacia*; MeSH Terms) AND (outbreak; MeSH Terms) AND (India; MeSH Terms) (Supplementary Material). Search terms like contaminated drugs or pharmaceuticals were not used as they would limit the search results.

Included were prospective, retrospective and cohort studies assessing Bcc outbreaks due to any source in Indian hospital settings. However, conference abstracts and case reports (less than 3 patients infected) were excluded. Studies that only reported the outbreak up to the point of identification, without investigating potential sources, were also excluded. This was based

on the rationale that without investigating the possible source, no valid conclusions can be drawn; neither would it substantially contribute to infection prevention strategies for avoiding such nosocomial outbreaks. We thoroughly documented essential details, encompassing outbreak features, patient population, nature of infections, investigation for infection source, and the implementation of infection prevention and control (IPC) strategies to manage the outbreak. 'Extrinsic contamination' of medical products is defined as the introduction of contamination during product utilization, while 'intrinsic contamination' refers to contamination occurring before use, specifically at the level of manufacturing[21].

Three reviewers (AS, SM, and LS) charted the data to extract data from the included studies. The table was created in two parts. First, the general characteristics of the published studies were charted with the following information: author, year of outbreak, city/State of India, number of patients affected, patient population, source of outbreak, type of *Burkholderia* species identified, infection type, and what method of molecular typing, if used, was done. The charted data was then rearranged according to a common denominator: the outbreak's source. Source categories were pharmaceutical preparations, medical products, environment, medical devices, and no source identified. The second table compiled the data of studies that successfully identified the source of the outbreak, and the relevant infection prevention and control (IPC) strategies used to curb the outbreaks. The assessment of potential bias and heterogeneity was not conducted. Basic statistical methods like percentages were used to summarize and communicate key trends in the data.

Results

For this analysis, our search identified 22 published studies of hospital-acquired *Burkholderia cepacia* complex outbreaks across India, which met our criteria (Table I)[12,15,16,19,20,22-38]. Ten outbreaks were reported from southern States of India[12,19,22,23-29] (6 from Tamil Nadu, 2 from Karnataka, 1 from Puducherry, & 1 from Kerala), six outbreaks were reported from western States[15,16,20,30-32] (5 from Maharashtra & 1 from Rajasthan), five from northern States[33-37] (2 from Delhi, 1 each from Haryana, Chandigarh and Jammu & Kashmir) and one from the eastern State of West Bengal[38].

Sources of Bcc outbreaks in India: Out of the 22 Bcc outbreak studies, a source could be identified in 17 studies while in five studies[29,30,32,34,38], no source was identified. The majority of the outbreak investigations (n=10) were concerned with pharmaceutical products, which included IV antiemetics granisetron[20] and palonosetron[25], topical anaesthetic eyedrops[22], upper surface of rubber stopper of sealed multidose amikacin vials[16], opened IV fluids[19,35] (5% Dextrose, normal saline), unopened and opened vials of caffeine citrate[31], diltiazem vials[23,24], cetrimide and chlorhexidine solution for skin antisepsis[15] and chlorhexidine mouthwash[35]. The source was identified to be distilled water used for nebulization and oxygen humidification in two studies[19,26]. The gel used during Ultrasonography (USG) was recognized as the source of the Bcc outbreak in four studies[12,27,28,37]. One study each was associated with contaminated water supply, including RO (reverse osmosis) water[33] and suction apparatus[36].

Among the identified sources of the outbreaks, the source was associated with pharmaceutical preparations in 45.4 per cent of the studies, the environment 13.6 per cent, medical products in 18.1 per cent, and devices in 4.5 per cent. Out of the 14 studies implicating medical and pharmaceutical products as culprits, intrinsic contamination was present in 10 compared to four outbreaks having extrinsic contamination.

General characteristics of the Indian Bcc outbreaks: Seven hundred and forty patients were affected across these 22 outbreaks. With pharmaceutical preparations as the source of the outbreak, the majority occurred in intensive care unit (ICU) settings as reported in five studies[15,19,23,31,35] involving 192 patients. Hospital wards were affected in three studies with a total of 80 patients, including chemotherapy day care unit[20], cardiology ward[24], and oncology ward[25]. One study reported a Bcc outbreak among 13 post-cataract surgery patients associated with anaesthetic eyedrops[22]. Another study reported an outbreak associated with contaminated rubber stoppers of amikacin vials, involving both paediatric ICU and ward[16], affecting 76 children. The majority of the patients were adults (n=266), where as paediatric population associated with pharmaceutical preparation-related outbreaks comprised 95 individuals. Among these 19 (20%) were exclusively confined to the neonatal intensive care unit (NICU). Out of the 10 studies, three mentioned outcomes in terms of mortality, which were nil (0/13) in Singhal *et al*[20], 27.6 per cent (21/76) in Mali *et al*[16], and 16.6 per cent (2/12) in Paul *et al*[19]. In one study by Lalitha *et al*[22] involving

Table I: Literature review of hospital outbreaks of *Burkholderia cepacia* complex in India

S. No.	Author	Year of the Outbreak	State of India	No. & patient population affected	Source	*Burkholderia* species isolated	Infection type	Molecular confirmation
Source: Pharmaceutical preparations (10)								
1.	Singhal *et al*[20]	2009	Mumbai, Maharashtra	13 Adults, Chemotherapy day care unit	Antiemetic granisetrone IV medication	*Burkholderia cepacia*	Bacteremia	Not performed
2.	Tandel *et al*[15]	2010	Pune, Maharashtra	12, Surgical ICU	Cetrimide + Chlorhexidine solution for skin antisepsis	*Burkholderia cepacia*	Bacteremia	Not performed
3.	Lalitha *et al*[22]	December 2011-February 2012	Madurai, Tamil Nadu	13, post-cataract surgery patients	Topical anaesthetic eye drops	*Burkholderia cepacia*	Endophthalmitis	BOX-PCR
4.	Mali *et al*[16]	June 2012-January 2013	Mumbai, Maharashtra	76, Paediatric ICU & Paediatric ward	Rubber stopper of amikacin vials	*Burkholderia cepacia* complex	Bacteremia	*recA* PCR & E-MLST
5.	Paul *et al*[19]	January 2014	Mangalore, Karnataka	12, NICU	Opened IV fluid 5% Dextrose, Normal saline & CPPV humidifier water (Also included in Environment category)	*Burkholderia cepacia*	Bacteremia	Not performed
6.	Shrivastava *et al*[31]	October 2015	Mumbai, Maharashtra	7, NICU	Unopened & opened vials of caffeine citrate	*Burkholderia cepacia*	Bacteremia	Not performed
7.	Fomda *et al*[35]	October 2017 -October 2018	Srinagar, Jammu & Kashmir	121, Surgical ICU	Unopened Normal saline, Chlorhexidine mouthwash	*Burkholderia cepacia*	Bacteremia	Not performed
8.	Sridharan *et al*[23]	February-March 2019	Chennai, Tamil Nadu	40, Cardiac care unit	Unopened vials of Diltiazem	*Burkholderia cepacia*	Bacteremia	Not performed
9.	Murugesan *et al*[24]	March 2019	Vellore, Tamil Nadu	11, Cardiology ward	Opened & unopened vials of Diltiazem	*Burkholderia contaminans*	Bacteremia	MLST
10.	Ghafur *et al*[25]	August-December 2021	Chennai, Tamil Nadu	56, Oncology ward	Antiemetic palonosetron IV medication	*Burkholderia cenocepacia*	Bacteremia	MLST
Source: Environment (2+1)								
11.	Rastogi *et al*[33]	April-November 2014	New Delhi	48, Neurotrauma ICU	Water supply & RO water	*Burkholderia cepacia*	Bacteremia, CLABSI, VAP	MLST

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S. No.	Author	Year of the Outbreak	State of India	No. & patient population affected	Source	*Burkholderia* species isolated	Infection type	Molecular confirmation
12.	Antony *et al*[26]	2016	Mangalore, Karnataka	3, Paediatric ICU	Distilled water used for nebulizers & humidification of oxygen	*Burkholderia cepacia*	Bacteremia	Not performed
Source: Medical products (4)								
13.	Solaimalai *et al*[12]	October 2016	Vellore, Tamil Nadu	7, Paediatric ICU	In-use Ultrasound gel	*Burkholderia cepacia* complex	Bacteremia	MLST
14.	Yamunadevi *et al*[27]	November 2016-January 2017	Chennai, Tamil Nadu	24, Cardiac care unit	Ultrasound gel	*Burkholderia cepacia*	Bacteremia	Not performed
15.	Dogra *et al*[37]	February 2020	Chandigarh	4, Paediatric surgical ward	In-use Ultrasound gel	*Burkholderia multivorans*	Bacteremia	MALDI-TOF, MLST
16.	Raj *et al*[28]	June 2018-December 2020	Thiruvananthapuram, Kerala	84, inborn nursery	In-use Ultrasound gel	*Burkholderia cepacia*	Bacteremia	Not performed
Source: Medical device (1)								
17.	Bharara *et al*[36]	March 2019	Gurgaon, Haryana	4, NICU	Suction apparatus	*Burkholderia cepacia* complex	Bacteremia	Not performed
Source: Not identified (5)								
18.	Bhise *et al*[30]	April 2013	Nagpur, Maharashtra	10, NICU	No source identified	*Burkholderia cepacia*	Bacteremia	Not performed
19.	Bhatia *et al*[34]	August 2015-July 2016	New Delhi	147, Various ICU's	No source identified	*Burkholderia cepacia*	Bacteremia	Not performed
20.	Gupta *et al*[32]	September-October 2016	Jaipur, Rajasthan	14, Oncology ward	No source identified	*Burkholderia cepacia*	CLABSI	Not performed
21.	Baul *et al*[38]	September 2016 – February 2017	Kolkata, West Bengal	29, Haemato-oncology ward	No source identified	*Burkholderia cepacia* complex	Bacteremia	PCR & PFGE
22.	Deb *et al*[29]	July-August 2019	Puducherry	5, (4 post-cataract & 1 post-keratoplasty)	No source identified	*Burkholderia cepacia* complex	Endophthalmitis	Not performed

CLABSI, central line associated bloodstream infection; CPPV, continuous positive pressure ventilation; E-MLST, extended multi-locus sequence typing; ICU, intensive care unit; IV, intravenous; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; MLST, multi-locus sequence typing; NICU, neonatal intensive care unit; PCR, polymerase chain reaction; PFGE, pulse field gel electrophoresis; RO, reverse osmosis; VAP, ventilator associated pneumonia

cataract surgery patients, 69 per cent (9/13) had a final visual acuity of 6/60 or better, 23 per cent (3/13) had a vision of perception of light and 7.6 per cent (1/13) had a final vision of 1/60.

Three outbreaks linked to environmental contamination occurred in neurotrauma[33], neonatal[19], and paediatric[26] ICUs, involving 63 patients. Of these, 48 were adults, and 15 were in paediatric age group. Two out of three studies mentioned outcomes in terms of mortality, nil (0/3) in Antony *et al*[26], and 16.6 per cent (2/12) in Paul *et al*[19]. Bcc outbreaks linked to medical products, specifically ultrasound gel, were reported in four studies. Two of these outbreaks involved ICU patients[12,27], while one occurred in a paediatric ward[37] and another in an inborn nursery[28]. Twenty-four adults were affected, whereas 95 were paediatric patients, of which 84 (88.4%) were neonates. Two studies out of four mentioned outcomes as 42.8 per cent (3/7) mortality by Solaimalai *et al*[12], and a case fatality rate of 26 per cent by Raj *et al*[28]. One study pinpointed suction apparatus[36] (medical device) as the source, involving four patients in the neonatal ICU, and the mortality rate was 25 per cent (1/4).

Outbreaks in which sources could not be identified, the majority occurred in ICU settings, as reported in two studies[30,34], involving a total of 157 patients. Oncology[32] and hemato-oncology[38] wards were affected in two studies with 43 patients. One outbreak was reported among five post-operative patients following cataract and keratoplasty surgery[29]. Outbreaks with no source identified affected 195 adults and ten neonates. Mortality outcomes were reported in two studies: Bhise *et al*[30] documented a rate of 30 per cent (3/10), while Baul *et al*[38] reported 3.5 per cent (1/28). One study by Gupta *et al*[32] reported the removal of central venous catheters as an outcome, with a rate of 71.4 per cent (10/14). In a study by Deb *et al*[29] involving five patients with endophthalmitis, the outcomes recorded were as follows: two patients achieved a best-corrected visual acuity (BCVA) of 20/60, two had a BCVA better than 20/200, and one patient had no perception of light.

In 20 studies, patients presented with Bcc bacteremia[12,15,16,19,20,23-28,30-38]. Out of these, two studies had central line-associated bloodstream infections (CLABSI)[32,33], and one study also reported ventilator-associated pneumonia (VAP)[33]. In the remaining two outbreak studies, endophthalmitis was the clinical presentation[22,29]. Only four studies specified the exact antibiotic treatment administered, while the rest stated that susceptibility patterns guided treatment without specifying the drugs. Ceftazidime in combination with meropenem/levofloxacin[12], and cotrimoxazole in combination with meropenem/ceftazidime[28] were used for treatment in one study each.

The species identified in 14 outbreaks was *Burkholderia cepacia*[15,19,20,22,23,26-28,30,31-35]. In five studies, *Burkholderia cepacia* complex[12,16,29,36,38] was identified, and *B. cenocepacia*[25], *B. multivorans*[37] and *B. contaminans*[24] was identified as the causative agent in three independent outbreaks. Bcc identification was performed using conventional phenotypic methods in seven studies[12,15,20,22,27,30,32]. Seven studies employed the automated Vitek 2 system[19,25,26,28,31,34,36], and five studies used Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)[23,24,29,35,37]. Additionally, *recA* PCR was used in two studies[16,33], and one study utilized the automated MicroScan panel for identification[38].

Molecular methods used for clonal association: Multi-locus sequence typing (MLST) was predominantly used to assess clonality in isolates for six outbreaks[12,16,24,25,33,37]. Other techniques, such as repetitive extragenic palindromic-polymerase chain reaction (PCR) (BOX-PCR)[22], pulse field gel electrophoresis (PFGE)[38] in one outbreak each, and MALDI-TOF[37] in another, were utilized to study clonal association. In 14 of the documented outbreaks, microbial typing was not conducted.

Management of Indian Bcc outbreaks: Various IPC strategies were used to curb the outbreaks (Table II). In most studies, contaminated stocks of pharmaceutical products were discarded. The concerned manufacturers were informed, and regular sterility testing was implemented[15,16,19,20,22-24,35]. The process of medication preparation and administration was strictly regulated[16,20,33,35]. Single-use IV fluids and replacement of multidose injection vials with single-use ampules were mandated[16,19,35]. Contaminated chlorhexidine was replaced with alcohol-based skin antiseptics[15]. Ventilator circuit cleaning was enforced[19].

Distilled water stored in the ICU meant for nebulization, humidification of oxygen and flushing feeding tubes was limited to a shelf-life of 24 hours[26]. Two outbreaks resulting from contaminated water sources were addressed through the application of chlorine, and calcium hypochlorite, respectively[33,35].

Sterile covers were employed on ultrasound probes as a preventive measure to mitigate direct contact between the gel and patient's skin[12,27]. The ultrasound

Table II: Patient population, source and infection prevention and control strategies implemented in Bcc outbreaks

S. No.	Author	Source of the outbreak	Patient population	IPC Strategies to control outbreak
1.	Singhal *et al*[20]	Antiemetic granisetron IV medication (Intrinsic)	Chemotherapy day care unit	Assessment of compliance with all infection control protocols Medication preparation & administration was regulated Use of only collapsible/closed intravenous fluid bags initiated Insertion process of ports was reviewed Day care unit was fogged & disinfected Results communicated to manufacturer; medication brand withdrawn
2.	Tandel *et al*[15]	Cetrimide + chlorhexidine solution for skin antisepsis (Intrinsic)	Surgical ICU	Contaminated stocks discarded Alternative use of alcohol-based antiseptics
3.	Lalitha *et al*[22]	Topical anaesthetic eye drops (Intrinsic)	Post-cataract surgery patients	Discontinuation of eye drops Notification of outbreak through All India Ophthalmology Association Long-term follow up of patients
4.	Mali *et al*[16]	Rubber stopper of multidose amikacin vials (Intrinsic)	Paediatric ICU & Paediatric ward	Documentation & communication of outbreak to paediatricians, medical store & administrative staff Batch of multidose amikacin injection vials discarded Replacement of multidose vials with ampoules Conforming to safe injection practices Enforcing strict adherence to hand hygiene
5.	Shrivastava *et al*[31]	Opened & unopened Vials of anti-apnoea drug caffeine citrate (Intrinsic)	NICU	Not mentioned
6.	Fomda *et al*[35]	Unopened Normal saline, Chlorhexidine mouthwash, outer rim of sinks water faucet (intrinsic & extrinsic)	Surgical ICU	Assessment done by IPCAT-H Onsite training in IPC & HAI surveillance 4 infection control nurses and 2 dedicated doctors hired to oversee IPC activities Medication & IV fluid administration was regulated Hand hygiene reinforced Single dose saline vials mandated Compliance to central line bundle care was assessed, use of femoral CVC's stopped Chlorhexidine mouthwash was discarded Water tank treated with high strength calcium hypochlorite
7.	Sridharan *et al*[23]	Unopened vials of Diltiazem (intrinsic)	Cardiac care unit	Alcohol hand rub installed at various places Diltiazem stock vials returned; drug company informed Policy to procure quality control check certificate for batches of all IV drugs
8.	Murugasen *et al*[24]	Opened & unopened vials of Diltiazem (Intrinsic)	Cardiology ward	Stock of Diltiazem vials discarded; results were communicated to manufacturer Hand hygiene reinforced Terminal cleaning advised As a part of quality assurance, sterility testing of all pharmaceutical products at regular intervals implemented
9.	Ghafur *et al*[25]	Antiemetic palonosetron IV medication (Intrinsic)	Oncology ward	Results communicated to Drug Controller General of India and manufacturer; medication brand withdrawn IPC strategies strengthened Tracked patients who received medication Central line and medication ports removed from patients with positive culture

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S. No.	Author	Source of the outbreak	Patient population	IPC Strategies to control outbreak
10.	Paul *et al*[19]	Opened IV fluid 5% Dextrose, Normal saline & CPPV humidifier water (Extrinsic)	NICU	Discarding stocks of IV fluids Replacement with single use IV fluids Enforcing intravenous line care & ventilator circuit cleaning
11.	Rastogi *et al*[33]	Water supply & RO water	Neurotrauma ICU	Infected patients cohorted by physical barriers into cubicles Cubicles fogged with hydrogen peroxide vapour Terminal cleaning of cubicles, bed rails & surroundings with quaternary ammonium compounds Hand hygiene reinforced Medication & IV fluid administration was regulated Cleaning and chlorination of water tanks Compliance to central line bundle care was assessed
12.	Antony *et al*[26]	Distilled water used for nebulizers & humidification of oxygen (Extrinsic)	Paediatric ICU	Fumigation Hand hygiene reinforced Screening ICU staff Cohorting infected patients Shelf life of distilled water stored in large containers restricted to 24 hours
13.	Solaimalai *et al*[12]	Ultrasound gel containers (Extrinsic)	Paediatric ICU	Cohorting infected children Hand hygiene reinforced followed by audit to check compliance Environmental disinfection Use of ultrasound probe cover was implemented
14.	Yamunadevi *et al*[27]	Ultrasound gel containers (Intrinsic)	ICU	Chlorhexidine used to wipe ultrasound gel Use of ultrasound probe cover was implemented Probe cleaned with alcohol spray between each patient
15.	Dogra *et al*[37]	In-use Ultrasound gel (Extrinsic)	Paediatric surgical ward	Not mentioned
16.	Raj *et al*[28]	In-use Ultrasound gel (Extrinsic)	Inborn-nursery	Withdrawal of contaminated multi-use USG gel Introducing practice of sterile single-use USG gel
17.	Bharara *et al*[36]	Suction apparatus (Extrinsic)	NICU	Cohorting of cases Suction bottles were cleaned with 2% glutaraldehyde solution Hand hygiene & IPC practices were reinforced

CPPV, continuous positive pressure ventilation; HAI, hospital acquired infection; IPCAT-H, infection prevention and control assessment tool for health care facilities; IPC, infection prevention and control practices; USG, ultrasonography

probe disinfection using an alcohol spray after each patient encounter was mandated[27]. Suction bottles in the neonatal ICU were cleaned with 2% glutaraldehyde solution[36].

IPC practices were assessed using the World Health Organization's IPC programmes in healthcare facilities (IPCAT-H)[35]. The education and training of the staff in IPC and hospital acquired infection (HAI) surveillance was done on-site. Compliance with central line bundle care was assessed[19,33,35]. Use of femoral CVC's was discouraged[35]. Infected patients were managed as appropriate and hand hygiene audits were conducted[12,16,24,26,33,35,36].

Discussion

This scoping review provides a comprehensive description of Bcc outbreaks in Indian hospital settings for the first time, encompassing all possible sources. This review highlights that these outbreaks majorly affect ICUs (57.1%). Patients in medical, surgical and trauma ICUs and those in paediatric wards and NICUs typically have lengthy hospital stay. They are subjected to various interventions, and their reliance on invasive medical devices and many broad-spectrum antibiotics makes them prone to bloodstream infections among others[39]. Outbreaks affecting ICUs were associated with different sources, including chlorhexidine solutions, amikacin and diltiazem vials,

dextrose and normal saline solutions, ultrasound gels, and suction apparatus. Bacteremia was noted to be the most common presentation, possibly stemming from a breach in the skin *via in-situ* central lines and catheters, contaminated IV medication and solutions, ultrasound gels used for routine scanning, and open wounds, among other routes. *Burkholderia cepacia* was observed to be the predominant species among the isolates, as conventional methods of bacterial culture and biochemical reactions for identification limit many laboratories in India. Other less commonly isolated species were observed to be *B. multivorans*, *B. contaminans* and *B. cenocepacia*.

Identifying the outbreak source is crucial for implementing effective infection control measures. We observed that investigators in one-fourth of the outbreaks could not identify the source. This may be due to challenges in identifying the bacterium, not having access to a special Bcc isolation medium or insufficient knowledge about potential reservoirs of Bcc, resulting in inadequate sampling during surveillance. However, we could determine that about 45.4 per cent of the reported studies were associated with pharmaceutical preparations (including sterile intravenous medications, solutions and disinfectants). Incriminated products were contaminated IV antiemetics granisetron and palonosetron, topical anaesthetic eyedrops, rubber stopper of multidose amikacin vials, IV fluids like 5% dextrose, normal saline, caffeine citrate vials, diltiazem vials, cetrimide and chlorhexidine solution and chlorhexidine mouthwash. We noted two outbreaks among cataract and keratoplasty surgery patients presenting with acute-onset postoperative endophthalmitis. A variety of perioperative and intraoperative sterile products used during eye surgeries are known to cause cluster endophthalmitis, such as intraocular lens solution, balanced salt solution, and others[40]. Topical anaesthetic eye drops were identified as the source of one of these outbreaks. The ability of Bcc to utilise a wide variety of organic compounds as carbon and energy source is a testament to the fact that it grows and thrives in sterile drug solutions, which are difficult to catabolize. Members of Bcc can oxidise aromatic and nitroaromatic compounds present in drugs, with the help of monooxygenase and dioxygenase enzymes. In pharmaceutical manufacturing, Bcc is believed to spread through water, raw materials and equipment surfaces, resulting in contamination of nonsterile products like mouthwashes, nasal saline solutions *etc*.,[10] as was seen in a Bcc outbreak by Bilgin *et al*[41] associated with contaminated chlorhexidine mouthwash. Once they contaminate the biocide, the most worrisome property of Bcc bacteria is their ability to grow and proliferate in these compounds. Resistance to disinfectants and antiseptics can be intrinsic or acquired. Various mechanisms include the presence of a highly charged lipopolysaccharide layer acting as a barrier; efflux pumps, notably of the resistance-nodulation-cell division (RND) transporter family acting against biocides like benzalkonium chloride and chlorhexidine gluconate[42,43], biofilm formation, and mutations in genes encoding cell wall, outer membrane proteins and porins. Bcc has been shown to contaminate analgesic gels and intravenous fentanyl in other reported outbreaks[44,45]. The presence of Bcc in drugs and solutions degrades the active compound and also contributes to the formation of toxic metabolites, potentially transmitting infection to vulnerable populations[10].

Contamination is often linked to breaches in IPC measures rather than intrinsic drug contamination, leading to delays in control efforts. This review shows that medical products like ultrasound gel should also be considered as possible source of infection during Bcc outbreak, as was seen in 18.1 per cent of the reported studies. USG scanning is routinely performed in intensive care, trauma and surgical units. Bcc species can degrade the stabilizing agent of ultrasound gels, that is, parabens (p-hydroxybenzoic acid esters), and hence contaminate the gel[46]. Intrinsic contamination of ultrasound gel has been reported when recovered from unopened vials[27]. We observed environmental contamination of water supply and distilled water as source of infection in 13.6 per cent of the included studies. The adaptive properties of Bcc hypothesized to facilitate growth in water include tolerance to limited nutrition, interaction with other bacteria, morphological switch to coccobacilli and temperature variations[18,42].

Among the studies where molecular testing was done, MLST was the most common (6/8, 75%) employed method for Bcc typing[12,16,24,25,33,37]. One study each utilised PFGE[38], BOX-PCR and MALDI-TOF as typing methods[22,37]. However, 14 studies did not conduct molecular analysis. They concluded their findings based on the phenotypic properties of isolating Bcc bacteria with similar antimicrobial susceptibility patterns, pinpointing a single common source and cessation of the outbreak after removing the source. MLST offers high resolution in distinguishing closely related strains, whereas PFGE is time-consuming and

less sensitive in delineating within species. MLST's digital sequence data aids computational analysis and data storage, contrasting with the visual banding pattern observed in PFGE, making it more subjective to interpretation[47,48]. Whole genome sequencing (WGS) has appeared to demonstrate superior discriminatory power in the recent past. WGS has a high cost and is time-consuming, restricting its availability[49]. MALDI-TOF emerges as a promising new technique with a high level of differentiation among species. Studies have shown good accuracy of MALDI-TOF in correctly identifying *Burkholderia* species and correlating well with molecular methods like PCR, proving a sensitive and rapid alternative[50,51].

Our review noted that most outbreaks where molecular typing was done were linked to a single sequence type. MLST identified a novel ST 824 in clinical and contaminated amikacin vial Bcc isolates[16], establishing an epidemiological link and confirming the outbreak source, marking the first such study in the country. Surprisingly, two reported outbreaks[33,37] involved the isolation of more than one Bcc species, possibly attributed to contamination with multiple *Burkholderia* species at the source. The average mortality rate documented for nine included studies was 18 per cent, exceeding the 10 per cent mortality rate noted by Hafliger *et al*[52]. However, many patients affected by *Burkholderia cepacia* complex infections in these outbreaks were in the ICU. They had multiple comorbidities, making it difficult to attribute mortality solely to the Bcc infection.

Commonly implemented IPC measures were observed, including product withdrawal, manufacturer communication, and regular sterility testing. Some studies also mentioned patient cohorting and hand hygiene regulation[33]. Specific measures included using single-use IV fluids, replacing multidose injection vials with ampules, substituting chlorhexidine with alcohol-based solutions, treating water tanks with chlorine, and employing sterile covers for ultrasound probes. We observed that outbreaks were more frequently associated with product contamination than medical devices (4.5%) or environment (13.6%). Similar findings were reported by Hafliger *et al*[52] where the environment (8.1%) and devices (17.1%) were far less commonly associated with Bcc outbreaks than contaminated products. Current hospital guidelines inadequately address the proper use of medical and pharmaceutical products, contributing to bacterial growth through factors such as using outdated products, storing for prolonged periods after use, improper storage conditions, and utilizing small dispensable bottles for mass-procured items like alcohol-based antiseptics and USG gels[10,53].

There are a few limitations in our scoping review. First, we focused exclusively on Indian studies. While this narrowed the evidence we could include, it allowed us to examine the role of contaminated pharmaceutical products and related manufacturing practices specific to India. Second, due to the paucity of limited published literature from India, we included case series involving 3-4 patients each and expanded our evidence beyond ICU outbreaks to include wards and daycare units. This review could not fully assess the overall heterogeneity of the included evidence. Third, we included some studies that did not provide detailed information on the infection prevention and control (IPC) measures implemented to contain the outbreak. Fourth, studies where the source of the outbreak could not be pinpointed but were investigated were also included.

Bcc, identified by the U.S. Food and Drug Administration (FDA) as the predominant contaminant in water-based pharmaceuticals, prompts guidance for manufacturers, alerting them of the risk and emphasizing screening before final release of product from the manufacturing unit[54,55]. A similar approach incorporated in good manufacturing practices (GMP) could help other countries as well.

Overall, this review highlights the importance of recognizing *Burkholderia cepacia* complex as an emerging group of bacteria responsible for serious life-threatening hospital-acquired infections leading to outbreaks in the healthcare settings. Identifying the infection source poses challenges due to Bcc's presence in diverse environments. However, thorough sampling, awareness of its pathogenicity and use of molecular typing methods can aid in this process. Implementing appropriate control measures post-source identification is crucial for outbreak containment.

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For correspondence: Dr Vikas Gautam, Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160 012, India
e-mail: r_vg@yahoo.co.uk