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State of the Science Review

Systematic review of ultrasound gel associated *Burkholderia cepacia* complex outbreaks: Clinical presentation, sources and control of outbreak

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Background: *Burkholderia cepacia* complex (Bcc) is an emerging opportunistic pathogen among immunocompromised patients. It frequently contaminates saline, fluids and ultrasound (US) gel used in hospitals. This systematic review was conducted to analyze Bcc outbreaks due to ultrasound (US) gel for better management of these outbreaks.

Methods: As per PRISMA guidelines, electronic databases "Embase" and "Pubmed" and "Web of sciences" were searched from 1991 to April, 2021 to identify studies causing *Burkholderia* spp outbreak due to contamination of US gels.

Results: The search identified 14 outbreak reports that met our inclusion criteria. Bacteremia was the most common clinical presentation in ten studies followed by urinary tract infections in 4 studies. In most of the studies *B. cepacia* was the most common isolated organism. Other members like *B. ambifaria, B. contaminans*, and *B. stabilis* caused outbreaks in two studies. Pulsed field gel electrophoresis and multilocus sequence typing were commonly employed methods to study the clonal association. In 8 outbreaks, intrinsic contamination of the gel, that is, contamination from manufacturing site, was present and 4 studies, extrinsic contamination, that is, contamination from environment was responsible for outbreak.

Conclusion: This review highlights the importance of US gel as a source of outbreak in health-care facilities. Ensuring sterility of US gel, sound epidemiological investigation of outbreak and prompt response by infection control team can prevent these outbreaks.

The members of the *Burkholderia cepacia* complex (Bcc) are Gram-negative bacilli which are increasingly being reported as opportunistic human pathogens.[1-3] Bcc rarely causes disease in immunocompetent individuals and is recognized as a serious pathogen in cystic fibrosis patients.[4] *Burkholderia* species are also reported as a major cause of sepsis.[5,6] Members of Bcc are intrinsically resistant to many disinfectants and antibiotics. These organisms are stable in the environment and contaminate mouthwash,[7] chlorhexidine solutions,[1] inhaled solutions,[8] moisturizing creams[9] and ultrasound (US) gels.[5] The contamination of these sterile medical solutions, especially US gels with Bcc has contributed to many outbreaks.[10] Hence, we conducted a systematic review to identify the mode of outbreak, risk factors and various infection control policies implemented to prevent these outbreaks.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed while conducting this study. We used the databases "Embase"(https://www.embase.com), "PubMed" (https://pubmed.ncbi.nlm.nih.gov), and "Web of sciences"(https://clarivate.com). We included literature published from 1991 to 18 April, 2021. Additionally, the reference lists of each included study were also screened (Fig 1). The following search terms and their combinations were used: (ultrasound gel OR jelly OR gel; MeSH Terms) AND (*Burkholderia cepacia* complex OR *Burkholderia multivorans* OR *Burkholderia* OR *Burkholderia* species; MeSH Terms) AND (outbreak). Prospective, retrospective, cohort and case-control studies, which assessed the outbreak of *Bcc* in the hospital setting were included. However, conference abstract, case reports or articles in languages other than English were excluded. The relevant information including characteristics of the outbreaks, type of infection among the patients, methods to identify the source of infection and infection prevention and control (IPC) policies implemented to control the outbreak were recorded. 'Extrinsic contamination' of medical

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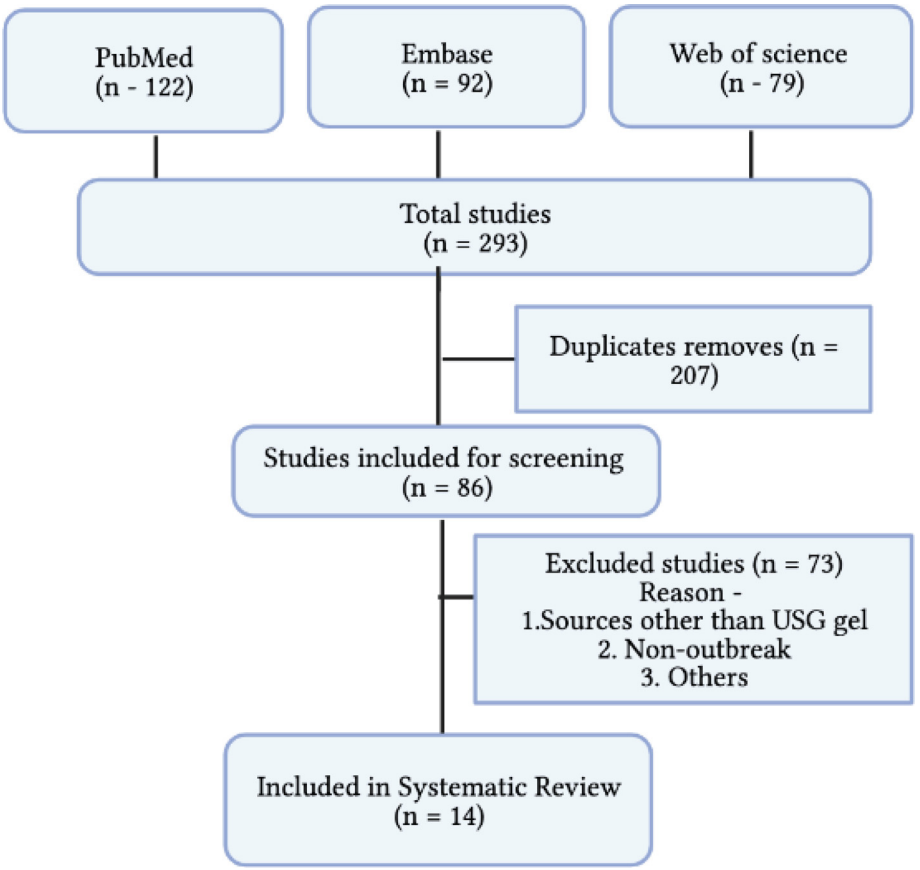

Fig 1. PRISMA flowchart for the inclusion of studies for the systematic review.

products was defined when contamination was introduced during product use, and 'intrinsic contamination' when the product was contaminated before use, that is, at manufacturer's site.

RESULTS

General characteristics of nosocomial Burkholderia cepacia *complex outbreaks*

In current analysis, on initial screening, 293 studies were found (Fig 1). The search identified 14 outbreak reports that met our inclusion criteria (Table 1).[5,6,11-14,10,15-21] Four outbreaks were reported from North America,[8,11,14,17] 3 from India,[5,6,15] 2 from China,[21,13] and one each from Saudi Arabia,[19] Kazakhstan,[12] South America,[16] Australia[18] and Austria.[20] Outbreaks limited exclusively to the intensive care unit (ICU) occurred in 5 studies.[15,6,18,19,5] ICU involvement along with wards was reported in 3 studies.[16,17,12] The total number of patients affected in all studies was 255. Bacteremia was the most common clinical presentation in ten studies[15,6,16,10,18,19,21,11,12,5] followed by urinary tract infections (UTI) in four studies[10,17,21,14] respectively. Other infections like intraperitoneal infection,[18] surgical site infections[13] and vaginitis[20] were reported in one outbreak study each.

Burkholderia cepacia was the most common isolated organism among the Bcc complex. Other members like *B. ambifaria, B. contaminans* and *B. stabilis* caused outbreaks in 2 studies.[16,17] In one study, both *B. multivorans* and *B. pseudomultivorans* were reported.[5]

Pulsed field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) were most common employed methods to study the clonal association among isolates. The PFGE was performed in 7 studies,[10,17,19-21,11,13] and MLST in 3 studies.[15,18,5] Other methods like repetitive extragenic palindromic-polymerase chain reaction (PCR) (rep-PCR),[16] Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)[5] and whole genome sequencing (WGS)[18] were employed to determine clonality in one study each. No bacteriological typing was done in three of the reported outbreaks.[6,12,14] Only 2 studies reported polyclonal association with the outbreak.[16,5]

Investigation and management of nosocomial Burkholderia cepacia *complex outbreaks*

All of the outbreak investigations concerned medical products, that is, ultrasound gel (Table 2). Infections due to Bcc was acquired in 5 studies among patients who underwent routine US imaging.[15,6,16,5,20] Other invasive procedures like US-guided transrectal prostate biopsy[10] and guided central venous catheter (CVC) insertion[18,19,11,12] led to outbreak in one and four studies respectively. Transthoracic/trans-fontanellar examination to study neonatal thoracic disorders/neuroanatomy was responsible for outbreak in one study.[16] In one study by Jacobson et al, infection was acquired either during routine blood pressure monitoring by Doppler US or diagnostic US after bladder exstrophy surgery.[17] It was observed that these gels were contaminated mostly at the site of the manufacturing. In 8 of the outbreaks, intrinsic contamination of the gel, that is, contamination from the manufacturing site,[6,16-21,13] was present. The extrinsic contamination, that is, from the environment was responsible for outbreak in 4 studies.[15,11,14,5] In 2 studies outbreaks gels got contaminated via both intrinsic and extrinsic sources.[10,12]

Many IPC measures were formulated. (Table 2) The contaminated batches of US gel were discarded in most of the studies.[16,14,5,19,21] Sterile covers were used for US probes to prevent the gel touching the patient's skin.[6] The US probes were cleaned with alcohol spray in

Table 1
Literature review of hospital outbreaks due to contaminated ultrasound gel by *Burkholderia spp*

S. No	Author (Reference)	Country	Year of the outbreak	Patient population affected (ward/ICU)	Procedure done using ultrasound gel	*Burkholderia* spp. isolated	Type of infection	Molecular typing method for confirmation
1.	Solaimalai et al[15]	India	2016	7 pediatric Patients (ICU)	Routine imaging by US	*Burkholderia cepacia* complex	Bacteremia	MLST
2.	Yamunadevi et al[6]	India	November 2016 -January 2017	24 adult patients (Cardiac-ICU)	Routine imaging by US	*B. cepacia*	Bacteremia	Not performed
3.	*Nannini* et al[16]	Argentina	April - July 2013	11 patients 7 - neonates (neonatal -ICU) 4 adults (3 in ICU 1 in ward)	Routine imaging by US including transthoracic and transfontanellar ones	*Burkholderia cepacia* complex (*B. ambifaria, B. contaminans* and *B. stabilis*	Bacteremia	Repetitive extragenic palindromic-PCR
4.	Hutchinson et al[10]	Canada	June - April 2002	6 adults patients (Ward)	Transrectal prostate biopsy	*B. cepacia*	Bacteraemia and urinary tract infection	PFGE
5.	**Jacobson et al**[17]	Canada	1993 -2003	40* Adult and pediatric patients (ICU and wards)	1. For assessing blood pressure by Doppler US, 2. Diagnostic US after bladder extrophy surgery	*B. cepacia* and *B. stabilis*	Urinary tract infection and other infections	PFGE
6.	Shaban et al[18]	Australia	March 26, - April 7, 2017	11 patients (ICU)	US-guided CVC insertion and other procedures	*B. cenocepacia*	Bacteraemia, urinary tract infection and intraperitoneal infection	MLST, Whole genome sequencing was performed on the Illumina NextSeq
7.	Abdelfattah et al[19]	Saudi Arabia	January 8, - June 15, 2016	14 adult patients (ICU)	US-guided CVC insertion	*B. cepacia*	Bacteraemia	PFGE
8.	Hell et al[20]	Austria	NA	8 adult patients	Routine US in obstetric patients	*B. cepacia*	Vaginal colonization. One patient developed vaginitis	PFGE
9.	Du et al[21]	China	March 19, 2018 and November 15, 2018.	71 patients (Wards)	Invasive operation or urological examinations	*B. cepacia*	Bacteraemia and UTI	PFGE
10.	Silmon et al[11]	United States	June-July, 2018	3 patients	US- guided peripheral intravenous catheter insertion	*B. cepacia*	Bacteraemia	PFGE
11.	Viderman et al[12]	Kazakhstan	March to August 2019	61 patients (ICUs and wards)	US- guided CVC insertion	*B. cepacia*	Bacteraemia	Not performed
12.	Wang et al[13]	China	May 2013	4 adult patients (ward)	Type-B ultrasonic inspection or continuous fetal heart monitoring	*B. cepacia*	Surgical-site infection	PFGE
13.	Garay et al[14]	Mexico, United States, North America		31 patients	Urinary catheter placement	*B. cepacia*	UTI	-
14.	Dogra et al[5]	India		4 pediatric patients (ICU)	Routine US	*B. multivorans* and *B. pseudomultivorans*	Bacteremia	MALDI-TOF, MLST

CVC, central venous catheter; ICU, Intensive care unit; MALDI-TOF, Matrix-assisted laser desorption/ionization-time of flight; MLST, multilocus sequence typing; PFGE, Pulsed field gel electrophoresis; PCR, polymerase chain reaction; UTI, Urinary tract infection; US, ultrasound; WGS, whole genome sequencing.

Table 2
Source and Infection prevention and control measures taken during the *Burkholderia cepacia complex* outbreaks

S. No	Author (Reference)	Source of outbreak: intrinsic or extrinsic	Outbreak control strategies instituted
1.	Solaimalai et al[15]	In-use US gel containers (Extrinsic)	1. Affected children were cohorted. 2. Stringent infection control measures, including hand hygiene were re-emphasized 3. Environmental cleaning and disinfection were done. 4. Hand hygiene audit was conducted to assess the impact of training. 5. Practice of using US probe cover was implemented in ICU
2.	Yamunadevi et al[6]	US gel- opened and unopened containers (Intrinsic)	1. Use of chlorhexidine to wipe the gel from the patient's body was done. 2. Practice of using US probe cover was implemented in ICU 3. US probes were cleaned with alcohol spray after use in every patient.
3.	*Nannini* et al[16]	In-use US gel containers (Intrinsic)	1. Removal of US gel stocks
4.	Hutchinson et al[10]	In-use 250-mL gel bottle used on the trans-rectal US probe (Extrinsic and intrinsic)	Sterile, single-use packets were used for any procedure whereby sterile body areas are entered.
5.	Jacobson et al[17]	US gel (Intrinsic)	1. Only sterile gel should be used 2. The 250-mL bottles were labeled with the date of opening, and expiration 3. Refilling of bottles and transportation of bottles between different units was prohibited
6.	Shaban et al[18]	US gel sachet. (Intrinsic)	1. The gel kits were removed
7.	Abdelfattah et al[19]	Contaminated US probe gel (Intrinsic)	1. The manufacturer and local authorities were informed. 2. The contaminated product was withdrawn from the hospital
8.	Hell et al[20]	US bottles (Intrinsic)	Not mentioned
9.	Du et al[21]	Single-use anesthetic gel (Intrinsic)	1. Hand hygiene audit was conducted to assess the impact of training. 2. Cleaning and disinfection of the endoscopes and cystoscope in outpatient room was strengthened. 3. Anesthetic gel product was recalled and withdrawn.
10.	Silmon et al[11]	US gel bottles (Extrinsic)	Importance of not refilling bottles was explained to staff.
11.	Viderman et al[12]	US gel (Extrinsic and Intrinsic)	1. All invasive procedures including central line catheterization was performed under sterile.
12.	Wang et al[13]	Type-B US probe samples, ultrasonic couplant (Intrinsic)	Not mentioned
13.	Garay et al[14]	US gel (Extrinsic)	Contaminated containers at warehouse and hospital were discarded.
14.	Dogra et al[5]	US gel (Extrinsic)	1. The contaminated US gel was withdrawn from regular usage. 2. The US probe cover was used for US screening and guided procedures.

between each patient use and chlorhexidine was used to wipe the gel from the patient's body.[6] Also, education of the staff for environmental cleaning and disinfection were conducted. Hand hygiene audits were conducted to assess the impact of training.[15,19] Procedures like CVC insertion were performed under sterile conditions.

DISCUSSION

Members of *Burkholderia cepacia* complex are increasingly been recognized and reported as an important pathogen in both immunocompromised and hospitalized patients.[1-3] Due to its intrinsic resistance to many groups of antimicrobials and disinfectants, it tends to survive in moist environments as is the case of hospital settings.[22] The cross-transmission of Bcc due to contaminated ultrasound gel in a health care facility is easy and worrying as it facilitates rapid spread of infections between different wards within the same hospital or between hospitals in different regions of a country.[23] Members of Bcc frequently contaminate ultrasound gel as it degrades the stabilizing agents, that is, parabens (p-hydroxybenzoic acid esters) used in the gel.[23] Bcc strains can thus survive as well as proliferate in US gels and this has led to outbreaks in hospitals.[10] Even intrinsic contamination of US gel can occur as this organism has been found in unopened vials.[6]

This review highlights the importance of identifying US gel as a possible source of infection. Routine examination by US is common in hospital settings. In surgical units, contaminated ultrasound gel can be a potential source for healthcare-associated infections like soft-tissue infections followed by bacteremia as open wounds and skin breach may be a conduit. In this review we observed bacteremia as the most common clinical presentation. We observed *B. cepacia* as the most common (71.4%) isolated species within the Bcc complex. However detection of other species like *B. stabilis, B. multivorans and B. psuedomultivorans* were less commonly isolated. The reason for this could be as many laboratories are limited by detection of *Burkholderia* to species level by conventional methods in many laboratories.

The US guided central line insertion can be the reason for bacteremia cases. Also, few studies reported Urinary tract infection (UTI) which could be due to use of US gels for urological examinations. The contaminated US gels provide access to sterile site in case of breach and use of invasive procedure. The current hospital guidelines are lacking regarding US gel. Many institutions purchase bulk containers of gel and dispense in small squeezy bottles (250-500 ml). The manufacturing and expiry dates are also not mentioned on these bottles. These bottles are re-warmed and used. All these factors promote growth and multiplication of *Burkholderia* spp. Since this is so common, single-use sterile ultrasound gel should strictly be used in critically ill patients especially prior to invasive procedures where US guidance is essential.

Great heterogeneity among Bcc typing methods was observed and while 50% of the studies used PFGE, one-fourth of studies had used MLST as the typing method. Identification of Bcc can be challenging as there is a risk of misidentification by commercially available phenotypic assays. PFGE is time-consuming and have less discriminatory

power to delineate within the species whereas MLST has better sensitivity to differentiate between species within the same genera. Currently, sensitive techniques like MALDI-TOF and WGS have shown high level of discrimination among genus of similar species and is recommended for accurate identification.[24] However, these newer techniques were used in only one study.[5,18] WGS is expensive and requires laboratory settings which is available only in minority of settings. MALDI-TOF has emerged as one of the rapid and sensitive method for detection as well as typing of the outbreak in comparison to WGS and MLST. Dogra et al. and Lambiase et al. analyzed the accuracy of MALDI-TOF and described a good correlation with molecular methods, making it a sensitive, rapid and cost-friendly alternative to assess clonality.[5,24]

We observed that most of the outbreaks were usually associated with a single clonal type. However, the isolation of multiple species of Bcc was a striking feature in two of the outbreaks.[5,16] The plausible explanation for this could be contamination of US gel with multiple species of *Burkholderia*. The Bcc species can form biofilms and contaminate the same environment.

Identification of source of outbreak and implementation of appropriate IPC response are the most important steps for outbreak control. It has been observed that Bcc is more often associated with contamination at manufacturers site (57.1%) in comparison to extrinsic contamination (28.5%).[25] Hafflinger et al also reported similar findings where manual contamination/environment was far less (8.1%) in comparison to contaminated products (17.1%) leading to Bcc outbreaks.[26] Thus these outbreaks are unlike MRSA outbreak where major vectors and source of infection are patients and health-care workers,[25] Thus demarcation between extrinsic and intrinsic route of contamination is important to prevent Bcc outbreaks. Consequently, the manufacturers should be warned and concerned healthcare facilities should be informed about the contaminated product.

CONCLUSION

This review highlights the importance of appropriate surveillance of outbreaks in controlling Bcc infection caused by contaminated ultrasound gel. Ensuring the sterility of US gel and strategies in order to prevent such outbreaks should be made in the institutions.

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