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Outbreak Report

An outbreak of *Burkholderia cepacia* complex exit site infection among peritoneal dialysis patients caused by contaminated spray dressing

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SUMMARY

Background: Wound dressing is intended to provide a physical barrier from micro-organisms. Spray dressing is convenient and can be applied to wounds of various contours. In July 2020, a cluster of four *Burkholderia cepacia* complex (BCC) exit site infections was identified among peritoneal dialysis patients in a regional hospital in Hong Kong. In response, our hospital infection control team conducted an epidemiologic investigation.
Methods: We conducted a retrospective cohort study of peritoneal dialysis patients with culture-confirmed BCC exit site infections from January 2011 to July 2020. Outbreak investigations, including case finding, molecular typing and post-outbreak surveillance, were performed.
Discussion: A substantial increase in BCC exit site infections has been observed since 2013, rising from 0.23 in 2012 to 1.09 episodes per 100 patient-year in 2015, with the number of cases in the first half of 2020 already surpassing the total from 2019. The potential source had been traced to a spray dressing introduced to exit site care in December 2012. *Burkholderia cepacia* complex was isolated from both the unopened and in-use sprays from the same lot. Multilocus sequence typing analysis confirmed their genetic relatedness. The spray dressing was subsequently removed from exit site care. Post-outbreak surveillance over two years showed a marked and sustained decrease in BCC exit site infection.
Conclusion: Water-based spray dressing can be a source of BCC causing wound infections. The use of contaminated spray dressing, especially in chronic wounds with proximity to indwelling catheters, may pose an inherent risk to patients.

Abbreviations: BCC, *Burkholderia cepacia* complex; CAPD, Continuous ambulatory peritoneal dialysis; ESI, Exit site infection; MLST, Multilocus sequence typing; ISPD, International society for peritoneal dialysis; PD, Peritoneal dialysis.

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Introduction

This is an outbreak report of *Burkholderia cepacia* complex (BCC) exit site infections caused by contaminated spray dressing used in routine exit site care among peritoneal dialysis patients in a regional hospital in Hong Kong.

Background

Burkholderia cepacia complex is a group of obligate aerobic, catalase-producing, glucose-nonfermenting, Gram-negative bacilli comprising at least 22 known closely related species [1]. They occur ubiquitously in natural environments such as soil and water, and can be found in plants as phytopathogens or biocontrol agents [2]. These organisms of low virulence do not usually cause diseases in immunocompetent persons. However, they have been extensively recognised as opportunistic pathogens. People at risk of infections on exposure to BCC include those with weakened immune systems, external medical devices, chronic lung diseases, namely cystic fibrosis, chronic granulomatous disease and those who inject drugs. Apart from pulmonary decline, pneumonia and life-threatening cepacia syndrome in cystic fibrosis patients, BCC can also cause bacteraemia, endocarditis, skin and soft tissue infection, bone and joint infection, and genitourinary tract infection in non-cystic fibrosis patients [3]. Virulence is divergent among, and even within, members of BCC. Mutant strains are observed to be more virulent, better able to survive within human macrophages [4,5], and more prevalent in cystic fibrosis chronic lung infections [6]. They are intrinsically resistant to multiple antibiotics and known to have highly variable antimicrobial susceptibility. Furthermore, no antimicrobial regimen has demonstrated superiority in treating BCC infections [7,8]. All of these pose therapeutic challenges in patient management.

Burkholderia cepacia complex can be transmitted through direct contact with infected persons, animals, plants, or environmental exposure. In 1966, an outbreak of postoperative urinary tract infections with BCC in children was traced to contaminated bladder irrigating fluid used during cystoscopy [9]. Since then, numerous outbreaks related to BCC in healthcare settings have been reported, of which 73.9% have a discernible source [10]. Various medications and devices have been implicated in these nosocomial BCC outbreaks, such as liquid docusate, alcohol-free mouthwash, anaesthetic eye drops, ultrasound gel, and respiratory therapy nebulisers [11—15]. Contaminated disinfectants, including povidone-iodine, chlorhexidine, and benzalkonium chloride, have also been repeatedly found to be the source of the outbreaks [16—18].

Presentation of outbreak

In July 2020, we identified an unusual cluster of BCC exit site infections involving four patients with end-stage renal disease on peritoneal dialysis over a two-month period from April to June 2020 in a tertiary regional hospital in Hong Kong. This retrospective study describes the outbreak investigation conducted by our local Hospital Infection Control Team and the subsequent location of contaminated spray dressing as the possible source of the outbreak. We also outline the observations in the post-outbreak surveillance after the implementation of control measures.

Setting

The outbreak occurred in an adult nephrology unit of a regional acute hospital in Hong Kong. The hospital is a major tertiary-care referral centre in Kowloon East Cluster with 1548 beds under the management of the Hospital Authority, serving an estimated population of 663,600 in Kwun Tong district, Kowloon. The nephrology unit involved provides care to 458 patients with end-stage renal disease on peritoneal dialysis as of December 2020. Swab culture from peritoneal dialysis catheter exit site was obtained by attending nephrologists as part of the routine diagnostic workup for exit site and tunnel infections. Swabs were inoculated onto blood and MacConkey agar at 36±1°C at 5% carbon dioxide and in ambient atmosphere for two days according to the standard operating procedures in our microbiology laboratory.

Epidemiological investigation

The Hospital Outbreak Control Team of Kowloon East Cluster actioned on 17th July 2020 when an unusual cluster of BCC in the exit site swab culture from the nephrology unit was detected by our microbiology laboratory in July 2020. We reviewed the culture records in the Laboratory Information System and clinical data in the electronic patient record system to evaluate the case trends of BCC exit site infection (ESI) over time. A case-patient was defined as any patient with end-stage renal disease having BCC isolated from peritoneal dialysis catheter exit site swabs from 1st January 2011 through 17th July 2020. Patients who had BCC repeatedly isolated from exit site swabs within a 12-month period were regarded as duplicates and excluded from the analysis, adapting from the definition proposed by Beckwith *et al.* in a retrospective cohort study [19].

We created a line listing of the case cluster and discussed in the infection control team meeting. A field investigation was conducted at the renal ambulatory care centre, where patients receive peritoneal dialysis training. We reviewed the local care practice of the peritoneal catheter exit site for common exposure liquid solutions. We collected both the liquid solution currently used by the index patients and the unopened one from the ward stock for culture. The samples were inoculated on tryptic soy agar plates and incubated at 36 °C for 18—24 hours. Colonies isolated on the agar were identified by matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry. For BCC, identification by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry is accurate only up to the genus level in view of vast intraspecific differences [20]. We used the disk diffusion method for the antimicrobial susceptibility testing according to Clinical and Laboratory Standards Institute standards [21]. All statistical analyses, including descriptive statistics and cross-tabulations, were performed using the IBM SPSS Statistics for Windows, version 22.0 (Chicago, Illinois, USA). Continuous variables were compared using the *t*-test, while categorical data were analysed using Pearson's chi-square test or Fisher's exact tests where appropriate.

Molecular typing

Multilocus sequence typing was performed in accordance with the multilocus sequence typing (MLST) scheme hosted in PubMLST databases to characterise the genetic relatedness of BCC isolates [22]. We typed the isolates using the sequences of internal regions of seven housekeeping genes: *atpD*, *gltB*, *gyrB*, *recA*, *lepA*, *phaC* and *trpB*. The sequence type profiles were generated based on the unique combination of MLST allele sequences on the curated databases. Clonality was established among BCC isolates exhibiting identical sequence types. Three archived BCC isolates from clinical specimens of different non-cystic fibrosis patients unrelated to this outbreak were included in the MLST analysis as controls.

Ethical considerations

This study has been approved by The Research Ethics Committee of Kowloon Central Cluster/Kowloon East Cluster of the Hospital Authority on 6th November 2023 (Ref: KC/KE-23-0157/ER-2). The study has been carried out in adherence to the ethical guidelines and principles in The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was not gained from patients involved in this outbreak. All patients were treated according to clinical judgement and infection control practices in order to treat them and control the outbreak according to local guidelines. Patients did not undergo randomisation or intervention for the purpose of this report. Data has been analysed and presented anonymously.

Results

From 1st January 2011 to 17th July 2020, a total of 42 patients with end-stage renal disease on peritoneal dialysis were identified to have BCC isolated from exit site swabs during workup for exit site or tunnel infections. On our retrospective review of records, an uptick in cases was seen since August 2013 (Figure 1). The incidence of BCC ESI has increased substantially from 0.23 episodes per 100 patient-year in 2012 to 0.63 episodes per 100 patient-year in 2013, then to 1.09 episodes per 100 patient-year in 2015 (Figure 2). The number of cases in the first half of 2020, at the time of the launch of the outbreak investigation, had already matched the total for the entire year of 2019.

The details of the case patients involved in the cluster were summarised in Table I. Those four patients were 50—67 years of age (median = 57.5 years), and half were female. All underwent continuous ambulatory peritoneal dialysis. Three of the patients had end-stage renal disease due to diabetes mellitus or hypertension, while one patient (patient 2) had renal failure caused by immunoglobulin A nephropathy. Immunosuppressive drugs were not prescribed within one month prior to infection in all of them. Only one patient developed the infection within the first year after the insertion of peritoneal catheter. None of the patients had BCC ESI, peritonitis or isolated from other body sites within the past six months. All four patients presented with signs and symptoms suggestive of ESI, such as the presence of purulent discharge or painful erythematous swelling at the exit site. While most patients had an uneventful recovery with antibiotic therapy alone, one patient (patient 3) had a complicated disease course and developed refractory BCC peritonitis, requiring hospitalisation and, eventually, peritoneal catheter removal. Patient 4 was admitted from emergency attendance for concurrent *Clostridioides difficile*-associated diarrhoea at the time of initial presentation of exit site complaints. None of the patients died of sepsis.

Peritoneal catheter exit site care practice adopted by the case patients was reviewed. All patients received training and assessment of care techniques by our nephrology nurses. According to the local guide on exit site care adopted by the renal teams of Kowloon East Cluster, chlorhexidine gluconate 4% w/v cutaneous solution is used to wash the exit site and surrounding skin. The exit site is rinsed well and pat dry. Following that, spray dressing of one recommended brand is applied at six and twelve o'clock position of the exit site and surrounding skin and allowed to air dry. In the end, dry gauze is fixed with surgical tape over the exit site as the final dressing.

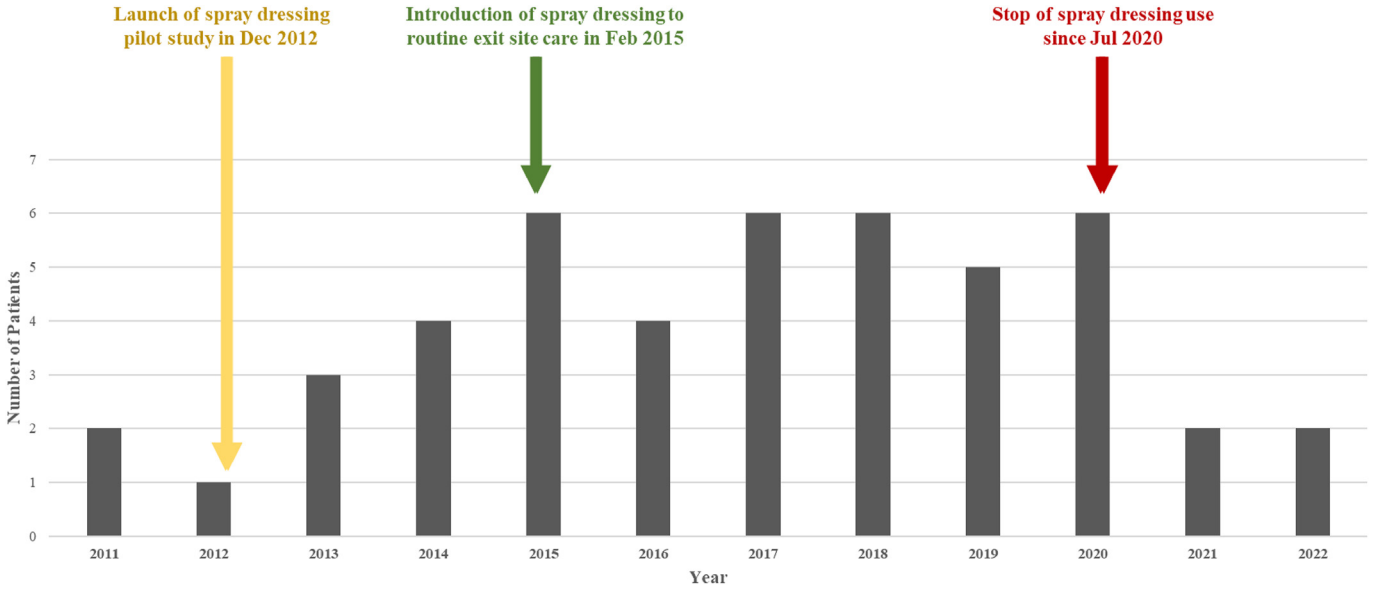

Figure 1. Number of patients who had bcc peritoneal catheter exit site infections in a Regional Hospital in Hong Kong from 2011 to 2022.

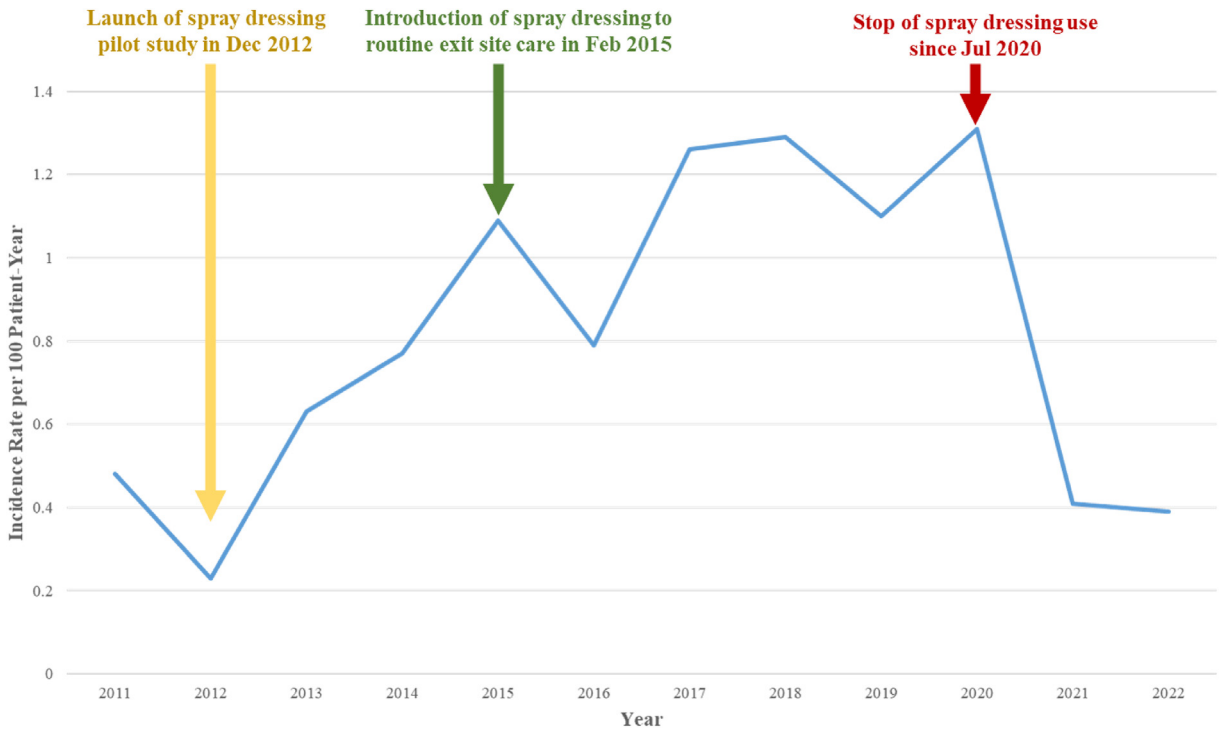

Figure 2. Incidence of BCC peritoneal catheter exit site infections in a Regional Hospital in Hong Kong from 2011 to 2022.

Their peritoneal catheter exit site care practice was thoroughly examined to identify any common exposure to potentially contaminated water-based materials. All patients reported good compliance with recommended practice with no use of items beyond specified. The chlorhexidine-containing solution was used only as liquid soap to work up a lather during cleansing. Afterwards, the exit site was immediately rinsed and washed with no intended residue. One patient (patient 4) actually had an allergic reaction to chlorhexidine and had only been using normal saline for cleansing as advised by the renal unit.

The only common aqueous exposure was traced back to the spray dressing in exit site care. The nanotechnology spray dressing was introduced into local practice in December 2012 as part of a pilot study. It was officially adopted in the recommended care guide by the renal teams in February 2015, after a published local study demonstrated its use in the reduction of ESI in peritoneal dialysis patients [23]. It contains 2% organosilicon quaternary ammonium salt as the active ingredient. The physical antimicrobial film is delivered in the form of fine mist spray towards the wound from a 30mL disposable plastic spray atomizer bottle, and immediately solidifies to form a positively charged polymer layer on the surface. It is marketed as a medical device, with product details including lot number, date of manufacture and expiry date displayed on the package label. According to the package insert, the spray dressing should be stored at room temperature, and the declared shelf life is three years.

In light of the exclusive common exposure, we collected the sprays in use by the case patients for sampling. Patients 2,3 and 4 were using sprays from the same manufacturing lot (lot B, date of manufacture: 5th September 2019, expiry date: 4th September 2022), while the spray of patient 1 was from a different lot (lot A, date of manufacture: 18th February 2020, expiry date: 17th February 2023). The spray solution was processed as previously described. Of note, 1mL of spray solution was added to 9mL of diluting buffer containing 3% Tween 80 before inoculation onto agar plates for disinfectant neutralisation. *Burkholderia cepacia* complex was found to be present in all three sprays from patients 2, 3 and 4, but not patient 1. In response, two unopened spray dressings from lot B were obtained from hospital ward stock and sent for culture. Growth of BCC was also detected in both samples.

The BCC isolates from patients 3 and 4, the sprays used by patient 2, 3 and 4 at the time of BCC ESI, unopened sprays from ward stock, and three isolates of BCC were submitted for MLST typing. We failed to include the isolate from patient 1 and 2 for analysis as the clinical specimen was discarded at the time of the outbreak investigation. The MLST allelic profiles and sequence types of the BCC isolates were presented in Table II. All the isolates detected in unopened and case patients' used sprays belonged to ST-102, which were different from the isolates from other clinical sources.

The Centre for Health Protection (CHP) of the Department of Health in Hong Kong was notified by the Hospital Outbreak Control Team. The joint investigation was conducted with the renal teams of Kowloon East Cluster, the Epidemiology and Surveillance Branch and the Infection Control Branch of CHP. The press release was published by CHP on 28th July 2020, announcing the epidemiological investigation findings and the association with the spray from lot B [24]. Members of the public were urged not to use the product for wound care due to possible bacterial contamination. The distributor had voluntarily conducted a recall of the affected lot from the market.

The post-outbreak surveillance was conducted in the renal unit for two years from the halt of the spray dressing. It was

Table I
Demographics and clinical features of patients with end-stage renal disease on peritoneal dialysis involved in the outbreak of BCC exit site infections

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years/gender	56/F	59/M	50/M	67/F
Aetiology of end-stage renal disease	Hypertension, type 2 diabetes mellitus	IgA nephropathy	Type 2 diabetes mellitus	Hypertension, type 2 diabetes mellitus
Other comorbidities	Hyperlipidaemia, nontoxic multinodular goitre	Erb's Palsy	Ischemic heart disease, autonomic dysfunction	Ischemic heart disease, bipolar disorder
Prior immunosuppressive drugs within one month	No	No	No	No
Time from PD catheter insertion to BCC ESI	3 months	2 years	3 years	4 years
Mode of peritoneal dialysis	Self-CAPD	Self-CAPD	Self-CAPD	Helper-assisted CAPD
Cleaning agents and dressing in daily exit site care	4% chlorhexidine gluconate liquid soap followed by nanotechnology spray dressing	4% chlorhexidine gluconate liquid soap followed by nanotechnology spray dressing	4% chlorhexidine gluconate liquid soap followed by nanotechnology spray dressing	Normal saline followed by nanotechnology spray dressing
Previous ESI or CAPD peritonitis in last 6 months	No	No	No	No
Isolation of BCC at other body sites in last 6 months	No	No	No	No
Date of symptom onset	22nd April 2020	2nd May 2020	9th April 2020	19th June 2020
Exit site symptoms	Peri-catheter erythema with serous discharge	Purulent discharge	Purulent discharge and granuloma formation	Pain and peri-catheter erythema
Complications	No	No	BCC peritonitis leading to loss of PD catheter	Antibiotic-associated diarrhoea caused by *Clostridioides difficile*
Outcome	Survived	Survived	Survived	Survived

observed that there was a significant drop in the incidence of BCC ESI among continuous ambulatory peritoneal dialysis (CAPD) patients after the implementation of control measures (Figures 1 and 2).

Discussion

We described an outbreak of BCC catheter-related infection among end-stage renal disease patients receiving continuous

Table II
Multilocus sequence analysis of the outbreak isolates and circulating clinical strains of BCC

Source of BCC isolate	MLST type	Allelic profile						
		atpD	gltB	gyrB	recA	lepA	phaC	trpB
Unopened spray dressing 1 (lot B)	102	64	80	76	89	105	97	70
Unopened spray dressing 2 (lot B)	102	64	80	76	89	105	97	70
Patient 2 spray dressing (lot B)	102	64	80	76	89	105	97	70
Patient 3 spray dressing (lot B)	102	64	80	76	89	105	97	70
Patient 3 peritoneal dialysis catheter tip	102	64	80	76	89	105	97	70
Patient 3 abdominal wound swab	102	64	80	76	89	105	97	70
Patient 4 exit site swab	102	64	80	76	89	105	97	70
Patient 4 spray dressing 1 (lot B)	102	64	80	76	89	105	97	70
Patient 4 spray dressing 2 (lot B)	102	64	80	76	89	105	97	70
Circulating clinical strain 1	2171	193	452	164	133	10	14	4
Circulating clinical strain 2	2172	169	193	1410	796	316	154	146
Circulating clinical strain 3	2173	15	11	1412	14	11	6	147

ambulatory peritoneal dialysis in Hong Kong, where a Peritoneal Dialysis First Policy is adopted [25]. The potential source of the outbreak had been traced to an antimicrobial spray dressing used in exit site care. Healthcare-associated infection outbreaks of BCC were often linked to liquid product contamination, owing to its preference for aqueous environments, survivability in nutrient-stressed conditions and resistance to certain preservatives [26,27]. Antiseptics and disinfectants are widely used in infection prevention and control to reduce microbial load on surfaces of living bodies and inanimate objects, respectively. Nonetheless, a systematic review concluded that 12% of nosocomial BCC outbreaks with identified sources were inadvertently caused by contaminated disinfection products, such as chlorhexidine and benzalkonium chloride [10]. Commonly used wound antiseptics such as povidone-iodine and chlorhexidine-cetrimide solutions have also been reported to contribute to infection and pseudoinfection outbreaks of BCC [16,28,29].

It is demonstrated that 28.2% of medical preparations implicated in the nosocomial BCC outbreaks were intrinsically contaminated [10]. Indeed, BCC was the microbial contaminant most frequently identified in the US Food and Drug Administration (FDA) recalls of sterile and non-sterile pharmaceutical products from 1995 to 2019 [30—32]. Water systems in manufacturing processes may be defective, and the microbiological quality of water may be adversely impacted by BCC [33—35]. At the time of COVID-19 pandemic, the quality of healthcare supply had been further jeopardised by a staggering increase in demand, disruption of operation and suboptimal quality assurance practices [36—38]. The FDA has published draft guidance for industry on microbiological quality during manufacturing and over the shelf life of non-sterile drugs. It is stated that there should still be a threshold of microbiological content for a non-sterile drug, beyond which patient safety and product efficacy may be compromised. It outlines recommendations for managing water quality, such as proper water system design and control, appropriate microbial action limits according to risk-based impact assessment, and routine water quality testing using validated procedures. The importance of conformity with Current Good Manufacturing Practice regulations was repeatedly emphasised [39].

Wound dressing is intended to provide a protective physical barrier to an open wound from microorganisms. On the other hand, as it comes into direct contact with a wound bed, there is an inherent theoretical risk of infection transmission if the dressing is contaminated. *Serratia marcescens*, *Burkholderia pseudomallei*, *Pseudomonas stutzeri*, *Clostridium tetani*, and fungi such as Zygomycetes and *Absidia corymbifera* have been implicated in outbreaks associated with contaminated wound cleansing and dressing materials. There is a prevailing belief that sterility is required in dressing application. It is, yet, challenged by the later introduction of the 'clean' concept [40—42]. Sleeves of non-sterile gauze dressings are often used in chronic wound care, particularly in non-infected wounds, due to their ease of use and affordability. There are no current published guidelines explicitly stating the definite requirements for sterility of dressings other than that for surgical wounds. It was mentioned that a surgical incision following primary closure is usually covered with a sterile dressing for the first postoperative 24—48 hours in the 1999 original Guideline for Prevention of Surgical Site Infection by the Centers for Disease Control and Prevention [43]. Postoperative incision care was not addressed in the subsequent guidelines update [44]. Dressing products are often registered under medical devices and are subject to regulatory controls that differ from those of other pharmaceutical products. Sterility testing and environmental monitoring are vital in ensuring the safety of these medical devices.

Film-forming spray has become the favoured choice of dressing in recent years because of its convenience and broad applicability to wounds of various contours. These liquid bandages are often formulated to contain antimicrobial substances that aim to provide extra wound protection. Nevertheless, their unique water-based nature and lenient storage requirements render these spray-on bandages at similar contamination risk by BCC to those pharmaceuticals with liquid base. In our reported outbreak, the probable infectious source was a nanotechnology-based spray dressing, which was proclaimed to have antimicrobial properties. To date, this is the first outbreak in the literature reported to be linked to such film-forming spray dressing. The apparently small number of cases might be due to low-level contamination of the products. Unfortunately, the release date of the affected lots to the market and their distribution among patient populations were unknown, making the estimation of exposed population and, therefore, the attack rate difficult.

Exit site care to mitigate peritoneal dialysis catheter-related infections has always been a subject of controversy. The recommendations on the care practice have been evolving through the years. Patients with end-stage renal disease are considered immunocompromised and at increased risk of infection. Catheter exit site is essentially a non-infected chronic wound. The fact that this chronic wound is in close proximity to a long-term indwelling peritoneal catheter, which is prone to biofilm formation, adds complexity to the already dire situation. There is a growing interest in the use of antimicrobial dressings to reduce local bioburden in wound management [45]. The International Society for Peritoneal Dialysis (ISPD) has recently updated its recommendations on peritoneal dialysis catheter-related infections [46]. The recommendation elucidates that it is not mandatory to cover the exit site with dressing after exit site care and topical antibiotic application beyond the immediate postoperative period, albeit with a Level 2 recommendation from low certainty evidence. The purported protective effect of dressing cover on catheter-related infection is found to be questionable on literature review [47—49]. The panel also underscored its caution about substandard dressing at risk for microbial contamination in the guideline recommendations, notwithstanding the potential benefits in preventing ESIs. Our outbreak accurately substantiates the concerns and provides basis of support for the latest ISPD recommendations. In addition, it is worth considering establishing surveillance of organism-specific peritoneal dialysis catheter-related infections, which can help detect clusters and outbreaks in a timely manner.

Conclusions

Water-based spray dressing can be a source of BCC causing wound infections. The use of contaminated spray dressing,

especially in chronic wounds with proximity to indwelling catheters, may pose an inherent risk to patients.

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Author contributions

Lily Shui-Kuen Cheng: Conceptualization, Formal analysis, Writing - Original Draft, Visualisation. **Sandy Ka-Yee Chau:** Supervision, Writing - Review & Editing. **Wai-Shan Chan:** Investigation, Data Curation. **Jonathan Hon-Kwan Chen**: Software, Validation. **Barry Kin-Chung Wong**: Methodology, Validation. **Kitty Sau-Chun Fung:** Resources, Data Curation.

Conflict of interest statement

None declared.

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