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Haemostatic discs demonstrate physical efficacy against microbes commonly associated with central-line-associated bloodstream infections

K.L. Gough [a,b], T.R. Dargaville [c], A.J. Ullman [d,e], N. Marsh [e,f], E.S. Pelzer [a,b,*]

[a] School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia
[b] Centre for Immunology and Infection Control, Queensland University of Technology, Brisbane, Australia
[c] School of Chemistry and Physics, Faculty of Science, Queensland University of Technology, Brisbane, Australia
[d] Centre for Children's Health Research, Children's Health Queensland Hospital and Health Services, Brisbane, Australia
[e] School of Nursing, Midwifery and Social Work, The University of Queensland, Brisbane, Australia
[f] Nursing and Midwifery Research Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia

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SUMMARY

Background: Vascular access devices form an essential component in the management of acute and chronic medical conditions. Introduction and ongoing management of these devices are linked with bundles of care aimed at reducing associated risks including bleeding and infection.

Aim: To evaluate the antimicrobial potential of the potassium ferrate haemostatic disc on Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) bacteria and on *Candida albicans*.

Methods: The impact of the potassium ferrate disc was compared with the often-used chlorhexidine gluconate (CHG) impregnated disc to evaluate the potential efficacy of the potassium ferrate disc as an alternative to CHG in cases with an increased risk of active bleeding.

Results: In the presence of anticoagulated blood, we observed an inhibitory effect of the haemostatic disc on microbial growth for microbial strains commonly associated with vascular access device related infections.

Conclusion: Our results indicate that the potassium ferrate disc may provide dual clinical benefits with both haemostatic and antimicrobial action observed during in-vitro testing.

Introduction

While essential, vascular access devices (VADs) are commonly linked to healthcare-associated harm, including post-insertion bleeding and infection-related sequelae [1,2]. Such devices are often used during the management of acute and chronic medical conditions in patients with complex medical conditions including compromised haemostatic function, leading to haemo-serous fluid loss at the access site, which compromises skin and dressing integrity. New portals of entry are also associated with local and systemic infection risks, including central-line-associated bloodstream infections

* Corresponding author. Address: School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, GPO Box 2434, Brisbane, Queensland 4001, Australia.
E-mail address: e.pelzer@qut.edu.au (E.S. Pelzer).

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(CLABSIs) [3,4]. The source of VAD-related infections is often endogenous, originating from migration of patient commensal skin flora along the access device or opportunistic pathogens from the patient microbiota or healthcare environment [5]. The combination of bleeding and infection risks requires ongoing assessment and management during VAD placement and removal, and for the duration of device time *in situ* [6].

Bleeding-related risks surrounding VAD insertion are routinely managed via haemostatic bundles, including careful device and site selection based on risk profile, insertion approach (e.g., ultrasound guidance), manual compression and site sealing [7,8]. Achieving haemostasis at the access site benefits the safety of the procedure by reducing dressing changes, site breakdown and infection risk. Skin injury is an adverse consequence of frequent application and removal of adhesive dressings, which further increases the risk of infection [9,10]. This iterates the importance of the development of a vascular access bundle that manages bleeding and infection risks simultaneously.

The skin is colonized by an endogenous microbiota associated with the superficial epidermis and extending into the dermal region via hair follicles and glands [11]. VAD infections commonly occur within seven to 10 days of device placement, following the migration of bacteria from the patient's skin surface towards the insertion site and intravascular space [12]. Even after topical antisepsis, endogenous microbiota rapidly repopulate the skin, resulting in microbial growth [13]. CLABSIs are also caused by external (non-host) causes of contamination. The most commonly isolated CLABSI agents are Gram-positive bacteria (especially coagulase-negative staphylococci, and *Staphylococcus aureus*), followed by Gram-negative organisms (including *klebsiella* and *pseudomonas* species), and then candida species [14,15]. Infections presenting within two weeks of device placement arise predominantly from extraluminal sources, and are predominantly caused by Gram-positive bacteria. Thereafter, intraluminal infections become more important, and are frequently biofilm-associated [16—19]. Infection prevention and control strategies are based on physical and chemical methods of control [20,21]. In the current era of antimicrobial resistance, the chief benefit of physical control methods lies in the effective reduction of microbial load without employing chemical control methods that are known to contribute selective pressures and further promote the emergence of pathogen resistance [12]. In this study we evaluated the physical efficacy of haemostatic discs, with the active agent potassium ferrate, against a series of established vascular access pathogens including Gram-positive and Gram-negative bacteria and *C. albicans*. Our evaluation included comparison with a commonly used chemical control, the chlorhexidine gluconate (CHG) -impregnated antimicrobial disc.

Methods

Determining the minimum inhibitory concentration of aqueous CHG against microbial strains

CHG minimum inhibitory concentrations

The minimum inhibitory concentration (MIC) of CHG against the Gram-positive bacterium *Staphylococcus aureus*, Gram-negative bacteria *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and the yeast *Candida albicans* was determined using the broth microdilution technique. Each test isolate was cultured overnight in tryptic soy broth (TSB) (Edwards Group; Cat No. 04269). Microbial suspensions were standardized at 0.5 McFarland turbidity using optical density. Aqueous 4% (22.5 mg/mL) CHG stock (Livingstone; Cat No. JJ61351LN) was pre-warmed to aid solubilization of the bisbiguanidide salt. Broth microdilution series were used to establish MICs for microbial strains exposed to CHG at concentrations ranging from 11.25 to 0.005 mg/mL. The microdilution series was prepared using two-fold dilutions of the 4% CHG and microbial suspensions were incubated at 37 °C and examined for visible turbidity at 24 h and seven days post-inoculation. Suspensions were sub-cultured on to tryptic soy agar (TSA) plates (Edwards Group; Cat No. 1335) to confirm inhibitory concentrations.

CHG and organic material MICs

Because vascular access sites commonly produce haemoserous exudate, MIC testing was also performed in the presence of varying percentages of organic material to assess the potential for inhibition of the antimicrobial effect of the CHG. Anticoagulated blood (Serum Australis; Cat No. HD500D) or glycerol solution ranging from 0 to 80% total diluent volume were used as organic material. The glycerol solution was standardized to an equivalent viscosity and density of anticoagulated blood and used as a negative organic material control, lacking the blood solids and proteins that react with the hydrophilic polymer and potassium ferrate in the disc to form an occlusive seal.

Differences in the MIC of CHG required to inhibit growth of the tested microbial species, were statistically analysed using R (v. 4.3.1) in R Studio (v. 2023.06.0; Build 421). Data normality was analysed with the Shapiro—Wilk's test. Within CHG, CHG and blood, and CHG and glycerol groups, the MIC was compared to determine whether this MIC was different depending on the CHG culture conditions. The significance of this difference was analysed using Kruskal—Wallis rank sum testing with follow-up pairwise Wilcoxon rank sum testing. MIC differences depending on the length of exposure were analysed using Wilcoxon—Whitney testing.

Disc diffusion assays to determine the zones of inhibition for haemostatic and CHG discs against select microbial strains

Disc saturation measurements

Titration experiments were conducted to establish the volumes of anticoagulated blood and glycerol solution required to saturate absorbent CHG-impregnated foam discs (BioPatch, Cat No. 44152). Briefly, liquid volumes ranging from 0.5 to 5.0 mL were pipetted into a syringe mounted in a valved acrylic block with a fabricated tunnel in which a triple lumen catheter (PowerPICC Provena 5; Cat No. S9385118) was inserted to mimic a vascular access site. CHG and haemostatic discs (StatSeal®, Biolife, Sarasota, FL, USA) were positioned around the cannula at the tunnel opening, and solutions were allowed to run freely through the tunnel, exiting the access site and making contact with the disc for 10 min.

Discs were weighed before and after fluid volume exposure via the acrylic block to establish the saturation point for the absorbent CHG disc, and to confirm that the haemostatic disc formed an occlusive seal when exposed to blood.

Zones of inhibition

The disc diffusion method was used to measure zones of inhibition (ZOIs) for the haemostatic and CHG discs [22]. Fresh overnight cultures in TSB were standardized at 0.5 McFarland turbidity using optical density. A 1-mL volume of microbial suspension was aseptically added to the surface of sterile TSA plates and allowed to absorb via diffusion. When completely dry, haemostatic and CHG discs exposed to no, low (0.5 mL) or high (3.0 mL) volume organic material (anticoagulated blood or glycerol solution) were placed on the surface of inoculated TSA plates, then incubated for 24 h and seven days at 37 °C in ambient atmospheric conditions. ZOIs were assessed, and annular radii measured to determine whether the discs had any inhibitory effect against the tested microbial strains.

In-vitro model

An in-vitro vascular access model was designed using a closed-tube system. The model was constructed using a model skin layer created with a bilayered sterile spot dressing floated atop medium inoculated with pure cultures of each of six microbial strains (representing Gram-positive, Gram-negative, and yeast control and clinical strains) standardized at 0.5 McFarland turbidity using optical density (Figure 1). Sterile 25-gauge needles attached to syringes were passed through the centre hole of blank, low-blood, or high-blood exposed haemostatic and CHG discs, piercing the dressing upon entry. The syringes were removed, and tubes capped prior to incubation in shaking incubators maintained at 37 °C for up to seven days. Cultures were performed with the dressing orientated with the apical surface in contact with the agar and the basal surface of the disc, to assess those areas that would be in contact with the haemostatic or antimicrobial disc/access site *in vivo*. This in-vitro model was designed to include a permeable access site and device, sheering forces, nutrient supply, blood exposure and incubation at core body temperature. Blood was not used as a diluent due to the production of coagulase by several of the tested microbial strains.

Ethical considerations

No human or animal subjects were used in the project. Ethics approval for use of animal tissue for the anticoagulated animal blood used in this study was obtained via a tissue use approval (AE TU 2023-6892-13650).

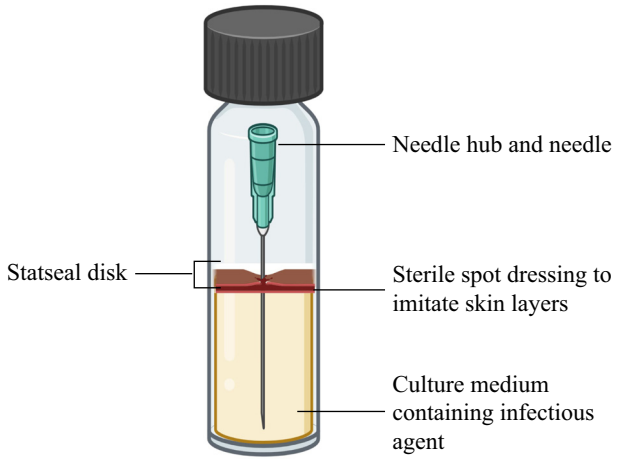

Figure 1. Diagrammatic representation of the in-vitro peripheral access model. Figure made using Biorender.

Results

MIC of aqueous CHG against microbial strains in the presence and absence of organic material

The presence of high proportions of organic material, either anticoagulated blood or glycerol solution, when combined with aqueous CHG increased the MIC values for each of the tested microbial strains (Table I). Kruskal–Wallis rank sum testing comparing the MICs required to inhibit growth of the six microbial species revealed a significant difference ($\chi^2(2)=12.048$, $P=2.42 \times 10^{-3}$) depending on whether species were cultured with CHG only, CHG and blood, or CHG and glycerol. Follow-up pairwise Wilcoxon rank sum testing indicated the MICs of CHG only were significantly lower than when combined with blood ($P=8.1 \times 10^{-3}$) and glycerol ($P=8.9 \times 10^{-3}$) (Supplementary Figure S1). There was no significant difference in the MIC between CHG and blood, and CHG and glycerol culture conditions. Furthermore, Wilcoxon–Mann–Whitney testing revealed the MICs required to inhibit growth of the six microbial strains was significantly lower one day post-inoculation, compared with seven days post-inoculation ($W=56$, $P=8.057 \times 10^{-4}$) (Supplementary Figure S2).

ZOIs for haemostatic and CHG discs against microbial strains

Volume titration experiment

The overall weight of the CHG discs increased by almost 100% of the weight of the volume added to the saturation point of 3 mL for anticoagulated blood and the control solution glycerol (3.06 ± 0.10 and 2.959 ± 0.11 g, respectively). In contrast, when exposed to either low (0.5 mL) or high (3 mL) volumes, haemostatic disc weight increased by an average of 0.17 ± 0.06 g and 0.31 ± 0.11 g, respectively. This consistent increase demonstrates the formation of an occlusive seal between the compressed hydrophilic polymer and potassium ferrate powder base of the disc and the blood. In the presence of glycerol, the compressed powder base formed an occlusive seal at low volumes but became emulsified at high-volume exposure in glycerol solution; therefore, overall disc weight increased by an average of 0.03 g and 0.05 g for low- and high-volumes, respectively.

The saturation point of 3 mL was then used for the high-volume experiment. The low volume of 0.5 mL was chosen based on titration experiments as it represented the minimum volume that could be effectively dispensed using the acrylic block model.

ZOIs

ZOIs were difficult to assess with the haemostatic disc given the zones of clearing were obscured by the foam outer and upper disc components, which cover the compressed powder base. The physical activity of the disc does not result in diffusion of disc components into the surrounding area. Therefore, the haemostatic discs were deconstructed after exposure to low or high blood volumes to facilitate more robust assessments of physical efficacy against various microbial strains.

Table I
Minimum inhibitory concentration of chlorhexidine gluconate (CHG) required to inhibit the growth of Gram-positive and Gram-negative bacterial strains, and the yeast *Candida albicans*

	Gram-positive				Gram-negative				Yeast			
	Staphylococcus aureus MSSA ATCC 14990		*S. aureus* USA300 MRSA		*Klebsiella pneumoniae* ATCC 8739		*Pseudomonas aeruginosa* clinical PA01		*Candida albicans* ATCC 1023		*C. albicans* clinical	
Days post-inoculation	1 day	7 days	1 day	7 days	1 day	7 days	1 day	7 days	1 day	7 days	1 day	7 days
CHG only	5	21	5	10	40	175	40	87	21	175	21	350
CHG + blood	70	>630	122.5	630	140	>630	>630	>630	52.5	>630	35	>630
CHG + glycerol	70	630	105	157.5	105	157.5	315	630	140	315	105	630

Minimum values recorded in the presence and absence of blood or glycerol (negative organic material control). All values recorded as CHG μg/mL. ATCC; American Type Culture Collection.

Subsequent removal of the haemostatic discs revealed complete clearance up to the edge of the disc bacteria *K. pneumoniae* (Figure 2), and *P. aeruginosa*, and Gram-positive *S. aureus* (MSSA ATCC 14990; MRSA USA300). This indicates potential for physical activity against infectious agents at the vascular access site and entire area of disc coverage.

Haemostatic discs produced consistent ZOIs following exposure to low and high blood volumes. The physical efficacy of the hydrophilic polymer and potassium ferrate compressed powder base of the haemostatic disc on the infectious agent remained the same or was slightly reduced over time, with ZOIs decreased between the 24-h and day-seven measurements (Supplementary Table S1). The haemostatic disc did not generate any inhibition against the strain of *C. albicans* of clinical origin but showed some inhibition for growth of the control strain at 24-h post-inoculation, inhibiting growth of the yeast beneath the disc, but with no extension beyond the disc edge for anticoagulated blood at low or high volume.

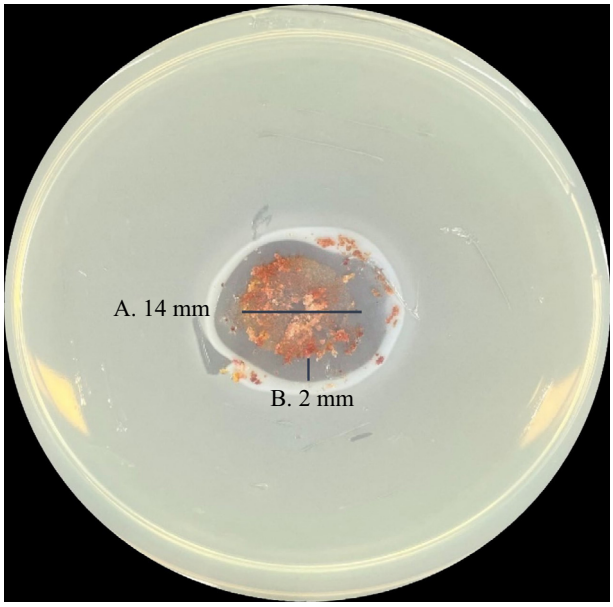

Figure 2. Zone of inhibition test for the haemostatic disc. Removal of a haemostatic disc shows complete inhibition of microbial growth observed as a zone of clearing beneath the disc (A) and extending beyond the edge of the disc (B) on TSA with a confluent lawn of *Klebsiella pneumoniae*. Given the physical mode of action of the disc, there is no absorption of solution, or product solubilization. Therefore, the disc remains almost dry during the incubation process, preventing diffusion of the hydrophilic polymer and potassium ferrate components, and limiting microbial inhibitory activity to a restricted zone beyond the disc margin.

Saturation of the CHG disc caused reconstitution and subsequent solubilized diffusion of solid CHG contained within the disc foam into the surrounding area. Therefore, in solid form, CHG in the disc does not appear to be diluted via exposure to liquid. ZOIs consistently increased for high-volume, compared with low-volume, anticoagulated blood, or glycerol fluid exposure to the CHG disc (Figure 3, Supplementary Table S1). ZOIs were consistently reduced for Gram-negative, compared with Gram-positive strains.

In-vitro model

After exposure to low or high volumes of anticoagulated blood, the physical efficacy of the compressed hydrophilic polymer and potassium ferrate powder base of the haemostatic disc was observed to extend to the edge of the compressed powder disc, and in some cases, extended beyond (results not shown). This suggests complete physical inhibition of infectious agents beneath the disc at the site of needle access. This observation was supported by growth of each microbial strains around the edge of the spot dressing where the disc was exposed to low or high blood volumes prior to incubation with *S. aureus* (MSSA ATCC 14990; MRSA USA300), *K. pneumoniae* (PA01), *P. aeruginosa* (ATCC 8739), and *C. albicans* (ATCC 1023). In the absence of exposure to any blood (blank disc), colonies were observed to grow around and on the surface of the spot dressings for all tested microbial strains and for *C. albicans* (clinical) exposed to low blood volumes.

CHG discs exposed to low and high volumes of blood also resulted in inhibition of microbial growth on the spot dressing and beneath the disc for *S. aureus* (MSSA ATCC 14990; MRSA USA300), *K. pneumoniae* (ATCC 8739), *P. aeruginosa* (PA01), and *C. albicans* (ATCC 1023). In the absence of exposure to any blood, colonies were observed to grow around and on the surface of the spot dressings for *K. pneumoniae* (ATCC 8739), *P. aeruginosa* (PA01) and *C. albicans* (clinical).

Discussion

The primary goal of this study was to assess the impact of the compressed hydrophilic polymer and potassium ferrate powder haemostatic disc (StatSeal®; Biolife) as an inhibitory agent against the growth of microbial strains commonly

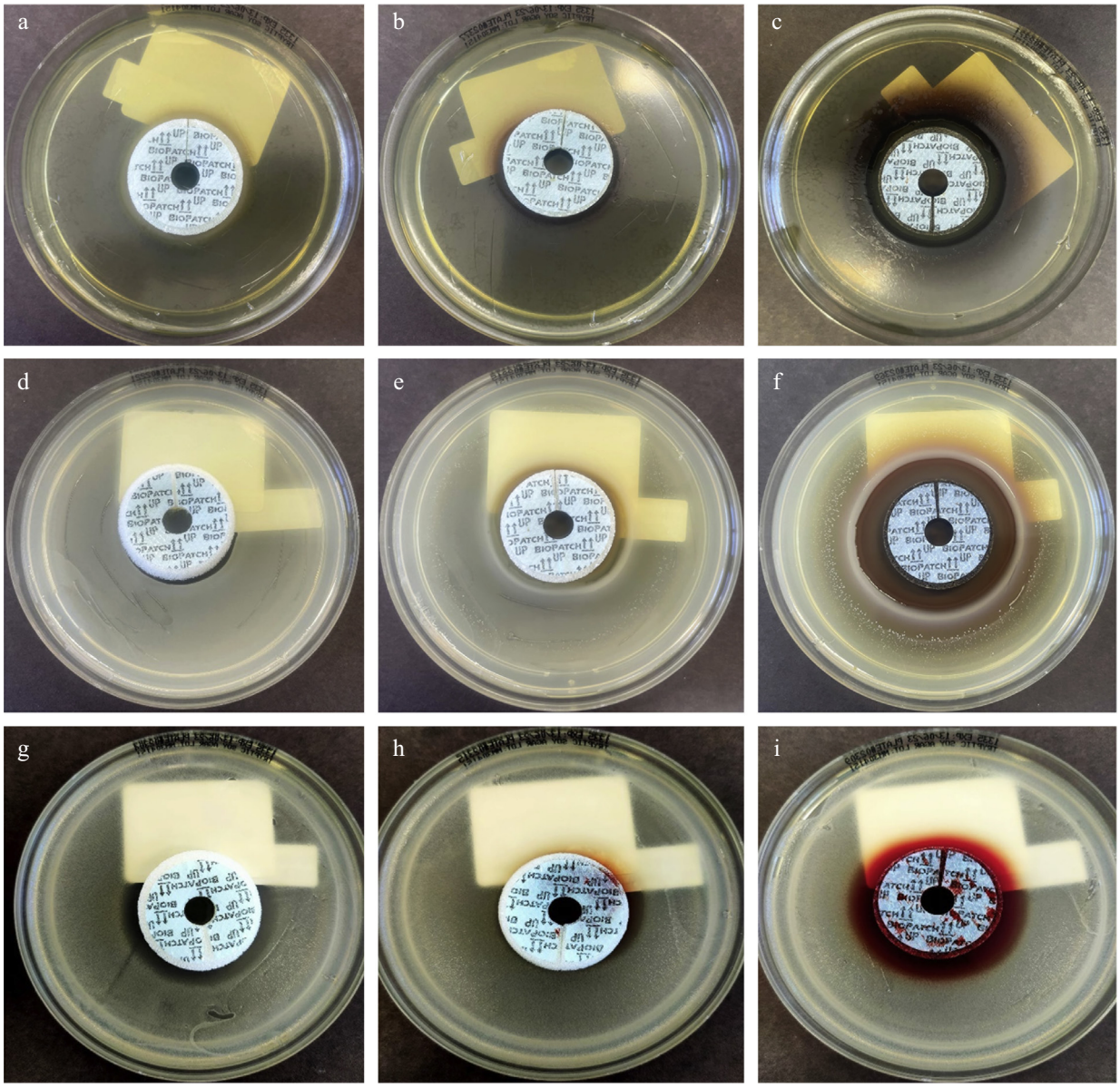

Figure 3. Zones of inhibition (ZOIs) for the chlorhexidine gluconate (CHG) disc. ZOIs were measured at seven days post-incubation for the Gram-negative bacterium *Pseudomonas aeruginosa* (PA01) and a blank disc (a), low volume (0.5 mL) blood (b), and high volume (3 mL) blood (c); ZOI for the Gram-positive bacterium *Staphylococcus aureus* (MRSA USA300) and a blank disc (d), low volume blood (e), and high volume blood (f); ZOI for the yeast *Candida albicans* (ATCC 1023) at 24 h post-incubation and a blank disc (g), low volume blood (h), and high volume blood (i). ZOIs increased with increasing absorption of blood by the CHG disc. ZOIs were measured as annular radii in millimetres.

associated with vascular access site infections. The haemostatic disc is often used in clinical practice to achieve rapid site closure for interventional cardiology and vascular procedures [23]. The compressed potassium ferrate powder disc effectively inhibited the growth of Gram-positive and Gram-negative bacteria of clinical significance in in-vitro testing. Based on this study, the physical activity of the compressed powder potassium ferrate supports a potential dual benefit for achieving rapid haemostasis coupled with reduced microbial growth. The results from our current study support further investigation of the potassium ferrate haemostatic disc in the context of microbial inhibition at vascular access sites.

To date, evidence of adverse reactions and contra-indications for the compressed potassium ferrate disc are lacking [8,24]. In contrast, CHG is reportedly associated with adverse outcomes including allergy, allergic dermatitis, local skin necrosis, and excoriation which have been reported in randomized controlled trials, observational studies and case reports [9,25,26]. Additionally, there is insufficient evidence to warrant use in short-term catheterization in paediatric patients, less than 2 months of age [27,28]. CHG dressings are not recommended for use in neonates due to the risk of serious adverse skin reactions [29,30].

The concentration of CHG impregnated in the antimicrobial disc (BioPatch™; Johnson & Johnson) far exceeds that required

for effective chemical inhibition of bacteria and yeast. However, evidence suggests that there is increasing tolerance to antiseptic agents including CHG, because of selective pressure associated with pathogen exposure to sublethal biocide concentrations in the environment [31—33]. Notably, the CHG disc showed limited effectiveness when dry, with significantly increased chemical inhibition of microbial strains in the presence of liquid volumes causing disc saturation and solubilization and release of the CHG embedded in the dry disc foam. As a biocide, CHG use is not negatively impacted by blood and body fluid contamination [34]. However, in this study we observed higher MICs associated with high proportions of CHG dilution by blood and organic material (Table I).

Increasing evidence suggests that widespread use of antiseptic agents is linked with the emergence of tolerant strains and cross-resistance to antibiotics including ampicillin, colistin, erythromycin and gentamicin [35,36]. The significance of cross-resistance against antimicrobial agents and a high prevalence of CHG-tolerant microbial strains causing CLABSI has been reported in the context of clinical exposure to CHG [37]. Whilst some microbial strains exhibit intrinsic resistance to CHG based on structural cell features, consistent with published literature, in this study, CHG also showed reduced efficacy against Gram-negative compared with Gram-positive bacterial strains [31].

The positive impact of infection-prevention strategies including antiseptic-impregnated dressings in CLABSI are well supported by reduced infection rates [38—40]. However, the benefits should be balanced with the long-term impact of widespread use of antiseptic agents associated with reduced susceptibility of infectious agents to existing antimicrobial treatments [31,32]. Alternatives to antiseptic agents including metals such as silver have been successfully utilized in wound care, and metal salts such as tellurite, which like silver exhibit direct interaction with infectious agents at the molecular level, are emerging as potential therapeutic alternatives to antimicrobial agents [41]. Resistance to these compounds is likely to be rare, because the mode of action against microbial cells renders the cell entirely non-viable. Ferrates are similarly effective antimicrobial agents at low-dose and contact times, exhibiting inactivation of Gram-positive and Gram-negative bacteria, spore-forming *Clostridia* and viruses, and have been shown to impair biofilm formation [42,43]. A ferrate-containing product combining haemostatic control and antimicrobial properties offers promise as a physical versus chemical control for reducing risks associated with infection-related sequelae in patients who require introduction of a vascular access device as part of their care.

Non-eluting medical products pose novel challenges for antimicrobial evaluation. In the context of this study, the instability of potassium ferrate in aqueous solution and the compressed powder composition of the potassium ferrate disc were limitations in testing the antimicrobial impact of the product using traditional microbiology tests including MICs and disc diffusion tests. In this study, we employed the disc diffusion test as a surrogate marker of toxicity, demonstrating a zone of clearing at the site of disc contact with a lawn of microbe, which reflects the position of the disc relative to the skin and endogenous microbiota in a clinical context.

In conclusion, compressed hydrophilic polymer and potassium ferrate powder discs show promise for inclusion in haemostatic bundles with antimicrobial benefits.

This study assessed the impact of the compressed hydrophilic polymer and potassium ferrate powder haemostatic disc (StatSeal®; Biolife), which is often used to achieve rapid site closure, as an inhibitory agent against the growth of several bacterial strains and the yeast, *Candida albicans*.

The StatSeal haemostatic disc shows physical inhibition against Gram-positive and Gram-negative microbial strains in the presence and absence of anticoagulated blood and organic material. The haemostatic disc performed better against Gram-negative *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* than CHG. CHG performed better against *Candida albicans* than the haemostatic disc.

The haemostatic disc performed better than CHG at low volume, with the CHG disc producing a more effective inhibitory result against infectious agents when saturated.

Author contributions

K.G.: conceptualization, methodology, formal analysis, writing — original draft. T.D.: conceptualization, methodology, writing — review & editing, formal analysis, funding acquisition. A.U.: conceptualization, methodology, writing — review & editing, formal analysis. N.M.: conceptualization, methodology, writing — review & editing, formal analysis. E.P.: conceptualization, methodology, formal analysis, writing — original draft, supervision, project administration, funding acquisition.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2023.12.006.

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