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The antimicrobial spectrum of Xeroform®☆

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ABSTRACT

Introduction/background: Xeroform® is a petrolatum-based fine mesh gauze containing 3% bismuth tribromophenate. Bismuth, similar to other metals, has antimicrobial properties. Xeroform® has been used for decades in burn and plastic surgery as a donor site dressing and as a covering for wounds or partial thickness burns. Despite this, the antimicrobial spectrum of Xeroform® remains largely unknown. We examined the in-vitro efficacy of Xeroform® against common burn pathogens using zone-of-inhibition methodology in a commercial research facility.

Methods/design: Pure strains of 15 common burn pathogens including Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-sensitive *Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Escherichia coli*, *Candida albicans*, Vancomycin resistant *Enterococcus*, *Acinetobacter baumennii*, *Klebsiella pneumonia*, Extended spectrum beta-lactamase producing *Klebsiella*, *Beta hemolytic Streptococcus pyogenes*, *Proteus mirabilis*, *Serratia marcescens*, *and Salmonella enterica ssp. Enterica* were inoculated at a strength of 10^6–10^{10} CFU/ml onto appropriate agar plates. A sterile 1 in^2 Xeroform® square was placed in the center of each plate, and the Zone of Inhibition (ZOI) was measured following 18-24 h of incubation at 37 °C.

A second bismuth pharmaceutical (bismuth subsalicylate, Pepto-Bismol®) was then tested using the same methodology against the same strains *of MRSA, MSSA, E. coli, K. pneumonia and S. marcescens*. Finally, 3% w/v bismuth tribromophenate in glycerol suspension was tested against 13 burn pathogens for antimicrobial activity independent of the Xeroform® dressing by measure of Zone of Inhibition.

Results/findings: For Xeroform®, none of the fifteen pathogens had a measurable zone of inhibition on any plate. Bismuth subsalicylate showed a zone of inhibition for MSSA in 3 plates (mean of 47.2 mm), in one of three plates for MRSA (13.8 mm), and in one of three plates for *S. marcesens* (89.6 mm). There was no zone of inhibition seen for *K. pneumonia* or *E. coli*. Bismuth tribromophenate, when not bound to Xeroform® showed activity against 12 of 13 pathogens.

Conclusions/implications: While bismuth subsalicylate, and bismuth tribromophenate unbound to Xeroform® demonstrate antimicrobial activity, it appears that Xeroform® dressings do not. The utility of Xeroform® in burn medicine may relate more to use as an impervious dressing than to antimicrobial effect. Donor sites are clean surgical wounds and

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clean partial thickness burns may have minimal colonization present. In such circumstances, an inactive and impervious dressing may be all that is necessary to promote wound healing.

1. Introduction

Xeroform® Gauze Wound Dressing (Covidien, Minneapolis, MN) is non-adherent wound dressing consisting of absorbent gauze covered with a petrolatum blend that includes 3% bismuth tribromophenate. Xeroform® dressings have been used for decades in burn care, wound care, and reconstructive surgery.

In burn practice, Xeroform® is commonly used to treat partial thickness burns [1–4] or as a covering over split thickness autografts [5–9]. Xeroform® has also been used over Integra® bilaminate skin substitute [10], over allograft [9], over cultured keratinocytes after initial takedown [11], for management of flap donor sites [12] and as a treatment for toxic epidermal necrolysis [13] or pyoderma gangrenosum [14].

Xeroform® is a dressing of choice for split thickness donor sites 'based on its low cost, ease of use, consistent rate of healing and low infection rate' [15,16]. Masella et al. in comparing 6 donor site dressings in a swine model found that DuoDerm® and Xeroform® were the most effective, and that Xeroform® was the "least expensive, easy to use and demonstrated rapid reepithelialization" [17]. As a standard of care, Xeroform® is commonly used as the control dressing in donor site studies [15,18–22] and has also been studied in combination with topical anesthetics [23,24].

Bismuth is a metallic element of atomic weight 83. Several elemental metals including mercury, silver, copper and zinc have antimicrobial properties, and certain bismuth compounds also show antimicrobial efficacy. Bismuth-3,4-dimercaptotoluene inhibits slime production by *Staphylococcus epidermis* [25]. Bismuth thiols suppress bacterial exopolysaccharide production by *Klebsiella* and *Pseudomonas* species preventing biofilm production [25]. Bismuth thiols are also bacteriostatic or bacteriocidal against several *Staphylococcus* species and have up to 1000-fold-greater antimicrobial activity than other bismuth salts [25]. Bismuth subsalicylate (Pepto-Bismol®) is used for the prevention and treatment of travelers' diarrhea and for the treatment of *Helicobacter pylori* infections [26].

The clinical utility of Xeroform®, along with the Gram-positive and Gram-negative efficacy of other bismuth compounds suggest that the bismuth tribromophenate present in Xeroform® might have broad antimicrobial properties. Data supporting this assumption is lacking, and for this reason, the following study was performed.

2. Methods

The antimicrobial properties of Xeroform® were tested in a commercial research facility, using zone-of-inhibition methodology as a screening test. All tests were run in triplicate. Pure cultures of fifteen common burn pathogens were plated onto appropriate agar media at targeted concentrations of approximately 10^7 colony-forming units (CFU)/ml. The pathogens, final concentration and culture media utilized are presented in Table 1. A one-square inch sterile Xeroform® square was

Table 1 – Burn pathogens evaluated against Xeroform®.

Pathogen	ATCC strain	Concentration	Media
Staphylococcus aureus (MRSA)	33592	6.00×10^9 CFU	Muller Hinton agar
Staphylococcus aureus (MSSA)	BAA-1721	2.58×10^8 CFU	Muller Hinton agar
Staphylococcus epidermidis	35894	1.50×10^9 CFU	Muller Hinton agar
Pseudomonas aeruginosa	27317	1.25×10^{10} CFU	Muller Hinton agar
Enterobacter cloacae	35549	1.20×10^{10} CFU	Muller Hinton agar
Escherichia coli	25922	9.25×10^9 CFU	Muller Hinton agar
Candida albicans	10231	6.00×10^7 CFU	Yeast Dextrose agar
Vancomycin-resistant *Enterococcus*	700802	1.00×10^6 CFU	Muller Hinton agar
Acinetobacter baumennii	14601	9.25×10^9 CFU	Muller Hinton agar
Klebsiella pneumonia	Porcine isolate	6.25×10^8 CFU	Muller Hinton agar
ESBL *Klebsiella*	700603	6.75×10^9 CFU	Muller Hinton agar
Beta-hemolytic *Streptococcus pyogenes*	15185	5.72×10^6 CFU	Tryptic Soy agar+5% sheep blood
Proteus mirabilis	21718	9.25×10^9 CFU	Muller Hinton agar
Serratia marcescens	14223	8.50×10^9 CFU	Muller Hinton agar
Salmonella enterica subsp. Enterica	39926	3.00×10^6 CFU	Muller Hinton agar

Note: ATCC=American Type Culture Collection (Manassas, VA).

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placed in the center of the agar plates. The plates were then incubated at 37 °C for 18-24 h. Following incubation, the zone of no-growth was measured around the test material to the nearest 0.5 mm and area of inhibition calculated by the formula (diameter/2)^2 × π.

A second experiment was then performed to confirm methodology by evaluating a different bismuth compound. Pure cultures of Methicillin-resistant *Staphylococcus aureus*, Methicillin-sensitive *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia* and *Serratia marcesens* were plated onto appropriate media in triplicate. An 8 mm diameter well was created in the center of the agar and filled with 200 μl of bismuth subsalicylate (Pepto-Bismol®). The zone of inhibition was then measured following 18-24 h of incubation at 37 °C.

Finally, attempt was made to test the antimicrobial properties of the base chemical unrelated to the Xeroform® dressing. Pure bismuth tribromophenate powder (CAS #5157-83-7) was obtained from a chemical supply house (City Chemical, LLC, West Haven CT) and tested as a 3% w/v suspension against several pathogens on agar plates. This proved more difficult than anticipated, because of the solubilities of bismuth compounds. Bismuth tribromophenate is insoluble in water but soluble in methyl and ethyl alcohols, ether, benzene, carbon tetrachloride, acetic acid, glycerol oils and strong alkalis. With exception of glycerol, all of the listed solvents would be expected to inhibit bacterial growth. For this reason, glycerol was chosen as the base solvent. Bismuth tribromophenate in glycerol, as well as glycerol alone was tested for zone of inhibition against 13 burn pathogens.

3. Results

Results are presented in Tables 2 and 3, and Figs. 1 and 2. For all fifteen burn pathogens tested, Xeroform® failed to produce a measurable zone of inhibition in any plate (Fig. 1).

Bismuth subsalicylate produced a zone of inhibition against Methicillin-sensitive *S. aureus* in all three plates (mean of 47.2 mm); against Methicillin-resistant *S. aureus*, in one of three plates (13.8 mm); and against *S. marcesens* in one of three plates (89.6 mm). There was no zone of inhibition produced in plates seeded with *K. pneumonia* or *E. coli* (Fig. 2 and Table 2).

Bismuth tribromophenate 3% w/v in glycerol, when tested independent of the Xeroform® dressing showed some antimicrobial activity, particularly against *Candida albicans*, Methicillin-resistant *S. aureus* and Methicillin-sensitive *S. aureus* (Table 3). With some pathogens, glycerol alone produced small zones of inhibition when tested separately. For this reason, corrected zone of inhibition data (zone of inhibition for bismuth tribromophenate+glycerol minus zone of inhibition for glycerol alone) was calculated and presented (Table 3).

4. Discussion

The contemporary delivery of burn care is increasingly evidence-based, however, a number of daily practices are still grounded in tradition. As an example, bacitracin is commonly applied to facial burns despite the fact that it covers Gram-

Table 2 – Burn pathogens evaluated against Pepto-Bismol®.

Pathogen	ATCC strain	ZOI # 1	ZOI # 2	ZOI # 3	Mean ZOI
Staphylococcus aureus (MRSA)	33593	0.0 mm	13.8 mm	0.0 mm	4.6 mm
Staphylococcus aureus (MSSA)	BAA-1721	53.5 mm	31.9 mm	56.4 mm	47.26 mm
Escherichia coli	25922	0.0 mm	0.0 mm	0.0 mm	0.0 mm
Klebsiella pneumonia	700603	0.0 mm	0.0 mm	0.0 mm	0.0 mm
Serratia marcesens	14223	0.0 mm	0.0 mm	89.6 mm	29.86 mm

Notes: ATCC=American Type Culture Collection (Manassas, VA), ZOI=Zone of inhibition.

Table 3 – Burn pathogens evaluated against Bismuth Tribromophenate.

Pathogen	ATCC strain	Corrected zone of inhibition*
Staphylococcus aureus (MRSA)	33592	413.00 mm
Staphylococcus aureus (MSSA)	BAA-1721	287.19 mm
Staphylococcus epidermidis	35894	88.50 mm
Pseudomonas aeruginosa	27317	97.73 mm
Enterobacter cloacae	35549	47.78 mm
Escherichia coli	25922	20.95 mm
Candida albicans	10231	539.24 mm
Vancomycin-resistant *Enterococcus*	700802	0.00 mm
Acinetobacter baumennii	14601	88.02 mm
Klebsiella pneumonia	Porcine isolate	80.35 mm
Beta-hemolytic *Streptococcus pyogenes*	15185	242.43 mm
Proteus mirabilis	21718	141.04 mm
Serratia marcescens	14223	59.55 mm

Note: ATCC=American Type Culture Collection (Manassas, VA).
* Corrected zone of inhibition=ZOI for bismuth tribromophenate 3% w/v in glycerol minus ZOI for glycerol for same species.

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Fig. 1 – Zone of inhibition data for Xeroform®.

positive flora and has no efficacy against common burn Gram-negative pathogens or yeasts [27]. The use of Xeroform® as a universal donor site dressing is another tradition. The active ingredient, tribromphenol-bismuth has been advertised as an antiseptic and wound care product under the Xeroform brand as far back as 1903 [28]. While the ideal donor site dressing remains to be defined, Xeroform® usually works well in this application.

The mechanism by which bismuth compounds exhibit antimicrobial properties is not understood [26,29,30]. Bismuth is known to attach to cell membranes [30,31,32] and studies of *Yersinia enterocolitica* treated with bismuth subsalicylate show bismuth deposited in the cell wall but not the cytoplasm [30,32]. In a similar fashion, *H. pylori* shows little or no intracellular accumulation of bismuth [30]. On the other hand, Mahoney et al., in testing 14 structurally simple bismuth compounds for efficacy against *Clostridium difficile* found that bismuth was rapidly incorporated and that intracellular bismuth was observed only with compounds possessing antibacterial activity [30]. Pitz et al. showed that when enterotoxigenic *E. coli* was treated with bismuth subsalicylate, bismuth binds to the bacterial membrane and also accumulates within the cell in as little as one half hour of exposure, an effect continuing over 24 h [31]. Marzano et al. note that the antibacterial action of bismuth drugs may involve enzyme inhibition as bismuth can inhibit fumerase (part of the bacterial tricarboxylic acid cycle), cytosolic alcohol dehydrogenase and urease [29].

While bismuth tribromophenate, bismuth subsalicylate and bismuth thiols show efficacy against certain pathogens, it appears that Xeroform®, as a composite dressing, lacks any demonstrated antimicrobial properties. Donor sites are clean surgical wounds and debrided partial thickness burns may have minimal colonization present. In such circumstances, an inactive and impermeable dressing may be all that is necessary to promote wound healing. Kempf et al. examined the cytotoxicity of 17 common burn care products using a cell-culture system and concluded that Xeroform® was among the least cytotoxic of all products tested [33].

In conclusion, clinical experience has shown that Xeroform® is a useful dressing for donor sites and other surgically clean wounds. Given the lack of any antimicrobial properties,

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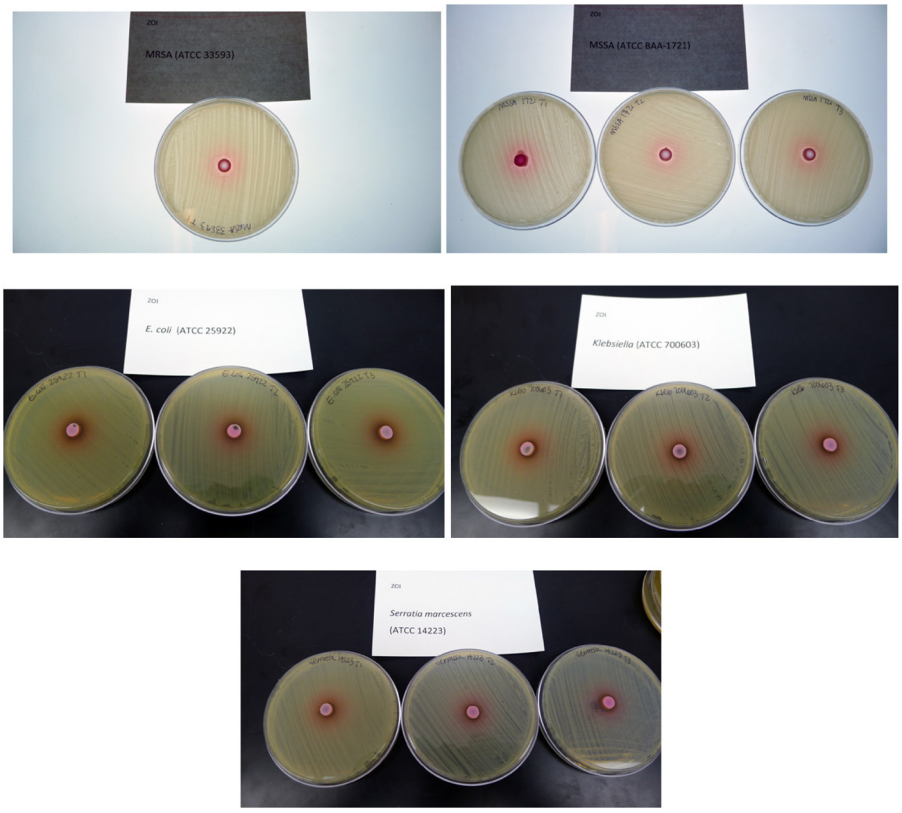

Fig. 2 – Zone of inhibition data for Pepto Bismol®.

Xeroform® would be a poor choice for the treatment of colonized or infected wounds. In such circumstances, excision or debridement, followed by the use of dressings with known antimicrobial properties would be more appropriate.

Disclosure

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