Skin Health

Management of Biofilm: The Efficacy of Controlled Release Iodine

Martha Roman, BS
Medline Industries, Inc

Problem

The skin is the body's largest organ and the first line of defense against pathogens. The skin provides a physical barrier, contains immune cells, and supports the growth of symbiotic microbes that aid in the prevention of pathogenic colonization.[1] Trauma and disease can weaken or break the skin's natural barrier abilities, facilitating the development of wounds and subsequent infection which impedes healing. In recent years, the body of knowledge on wound infection has advanced significantly, and the importance of wound biofilm to the wound infection continuum has been widely recognized.[2] The presence of biofilm stalls wound healing and contributes to wound chronicity and reduced antibiotic susceptibility.[3,4] The impact of biofilm is widespread; over 90% of chronic wounds and 6% of acute wounds contain biofilm.[5, 6]

In the United States, chronic wounds impose substantial economic burden, with an estimated cost of $28 billion annually alone,[7] further emphasizing the importance of developing new methods and treatment strategies to eradicate infection and promote healing.

Why Iodine?

Clinicians have a wide variety of products at their disposal which are designed to combat infections and thus remove barriers to wound healing. However, few technologies have as long of a history of clinical use as iodine-based therapies. Iodine has been used as an antibacterial for centuries and has been incorporated over the years into a range of wound dressings used routinely in treatment of chronic wounds. The iodine products of today release iodine from iodophors, which are compounds in which iodine is complexed with a temporary "carrier" to provide for a gentler, controlled release that maintains efficacy against bacteria. Even at low concentrations, the antibacterial action of iodine is quick, but the exact antibacterial mechanism of action of iodine is unknown. One potential mechanism involves Iodine rapidly penetrating cell membranes and disrupting proteins, enzymes, nucleotides, and fatty acids in the cytoplasm and cytoplasmic membrane, leading to cell death.[8, 9] Iodine's multiple modes of action ensure the rapid kill of microbes and help prevent the development of bacterial resistance. It has also shown significant efficacy against a variety of biofilm strains in in vitro and ex vivo models.

Biofilms are bacterial structures physically attached to a surface and characterized by significant tolerance to antibiotics and biocides. Various biofilm models have been developed to simulate aspects of a wound environment, often incorporating clinically relevant microbes, in which the antibacterial efficacy of wound dressings can be compared. Diverse, complex polymicrobial communities consisting of bacteria reside in wounds. In chronic wounds, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are amongst the most prevalent opportunistic, pathogenic bacterial species that are the most frequently isolated yeasts from polymicrobial chronic wounds.[10-12]

Iodine-based wound dressings have been tested in a comparative manner against other commonly used wound dressings such as silver based therapies. In an in vitro flatbed perfusion biofilm model, an iodine dressing was found to be more efficacious against both 24 hour *P. aeruginosa* and 24 hour *S. aureus*. The iodine dressing had a sustained antibacterial effect throughout the treatment period, reducing the biofilm levels of each organism below minimum detection levels after 24 hours.[13] In an in vitro constant depth film fermenter, a multispecies biofilm including *P. aeruginosa* and *S. aureus* was grown for 3 or 7 days. Both the povidone-iodine dressing and another controlled release iodine dressing showed complete disruption of the bacteria in the biofilm after 7 days of treatment.[14] Another study comparing the efficacy of other dressings on biofilm, involved an in vitro porcine explant model that found controlled release iodine dressings decreased mature, 3-day *P. aeruginosa* by eight logs after one and three days.[15] In an ex vivo porcine skin model, five types of commonly used wound dressings were assessed for their antibacterial efficacy against *P. aeruginosa* biofilm grown for 3 days and pre-treated with antibiotics. Controlled release iodine demonstrated a 7 log kill of mature 3-day *P. aeruginosa* biofilm after 24- and 72-hour exposure.[16] While all of these studies included a variety of silver dressings, iodine dressings largely outperformed silver dressings in overall log kill.

A systemic review of topical agents used for managing chronic biofilm infections included 43 articles (47 studies: 39 in vitro, 5 in vivo animal, and 3 human).[17] Twelve topical agents were identified: silver, honey, iodine, polyhexamethylene biguanide (PHMB), poloxomer 188, superabsorbent polymer, melaleuca oil, hypochlorous/acetic acid, pyridine, chlorhexidine, ringer's solution, and electroceutical. The in vitro results indicated iodine had the highest mean log10 reduction (4.81±3.14) of biofilm out of all agents. Although all agents demonstrated lower efficacy against biofilm in the animal studies, iodine still had a 4.5 log reduction, which reinforces its possible efficacy in a clinical setting. Since no single biofilm model perfectly mimics the wound environment, efficacy against biofilm in various models, both monospecies and polyspecies and of different maturities, highlights the strong effect of iodine dressings.

Table 1: Effects of Various Dressings against Biofilm (in vitro or ex vivo studies)

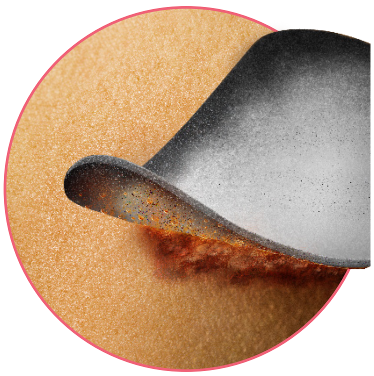
If multiple log reductions are listed then the log reduction correlates with the treatment time in the table.

Model	Organism/Maturity	Treatment Time	Treatment	Log Reduction
Flatbed Perfusion Biofilm Model[13]	*P. aeruginosa* 1 Day maturity	5, 8 and 24 hours	Iodine	~2.5, ~4, ~7.25
			Silver	~3, ~4, ~3
	S. aureus 1 Day maturity	5, 8 and 24 hours	Iodine	~2, ~4, ~7.25
			Silver	<1, <1, <1
Fermenter[14]	*P. aeruginosa / S. aureus* 3 Day or 7 Day maturity	7 days	Controlled Release Iodine	~8
			Povidone Iodine	~8
			Various Silver	NS
Pig Explant[15]	*P. aeruginosa* 3 Day maturity	24 hr, 72 hr	Controlled Release Iodine	~8, 8
			Povidone Iodine	1.5-2
			Polyethylene Nano crystalline silver	3
			Ionic Silver	NS
			0.2% PHMB	NS
Pig Explant[16]	*P. aeruginosa* 3 Day maturity	24 hr, 72 hr	Controlled Release Iodine	7.827, 7.77
			Povidone Iodine	2.571, 1.113
			Ionic Silver CMC	0.374, 0.801
			Polyethylene Nano crystalline silver	1.822, 1.31
			PHMB	0.439, 0.465
			Honey	1.555, 0.352
			Ethanol	1.351, 1.285
Systemic Review: in vitro[17]	Various	24 hr	All Iodine Agents	4.81 (±3.14)
			All PHMB	3.33 (±2.28)
			All silver agents	2.18 (±1.81)
			Poloxamer 188	3.71 (±2.37)

IoPlex and Biofilm

IoPlex with I-Plexomer™ is the world's only controlled release iodine foam dressing, Figure 1. Ioplex is an iodophor of iodine and a specially modified foam polymer. The proprietary controlled-release system allows for regulated and sustained infection management through the slow release of iodine within the wound dressing. As iodine is released, the dressing changes from black to white.

Figure 1: Ioplex Iodophor Foam Dressing



- Sustained release over 24 to 72 hours
- Can be cut to shape of wound and stacked

In order to determine the antibacterial time-kill effectiveness of IoPlex, in vitro antibacterial barrier testing was performed. IoPlex was challenged with *P. aeruginosa* for 30 minutes and Methicillin Resistant *Staphylococcus aureus* (MRSA) for 5 minutes, 30 minutes, 3 days, and 7 days. For all of the above organisms and time points, IoPlex demonstrated a greater than 4-log kill against MRSA within 5 minutes and P. aeruginosa within 30 minutes, sustained for 7 days.[19]

An in vitro CDC bioreactor biofilm model was implemented to evaluate the efficacy of Ioplex. Mature *S. aureus* and *P. aeruginosa* biofilms were grown for 24 hours. After one day of treatment, IoPlex had an 8-log reduction against both *S. aureus* and *P. aeruginosa* biofilms, Figure 2.[20] A 12-well plate anaerobic direct contact model evaluated IoPlex's efficacy against 48-hour *Bacteroides fragilis* biofilm. After one day of treatment, IoPlex had a 6-log reduction of *B. fragilis* biofilm, Figure 3. Overall, IoPlex outperformed all other tested dressings.[21]

Figure 2: In Vitro CDC Bioreactor Biofilm

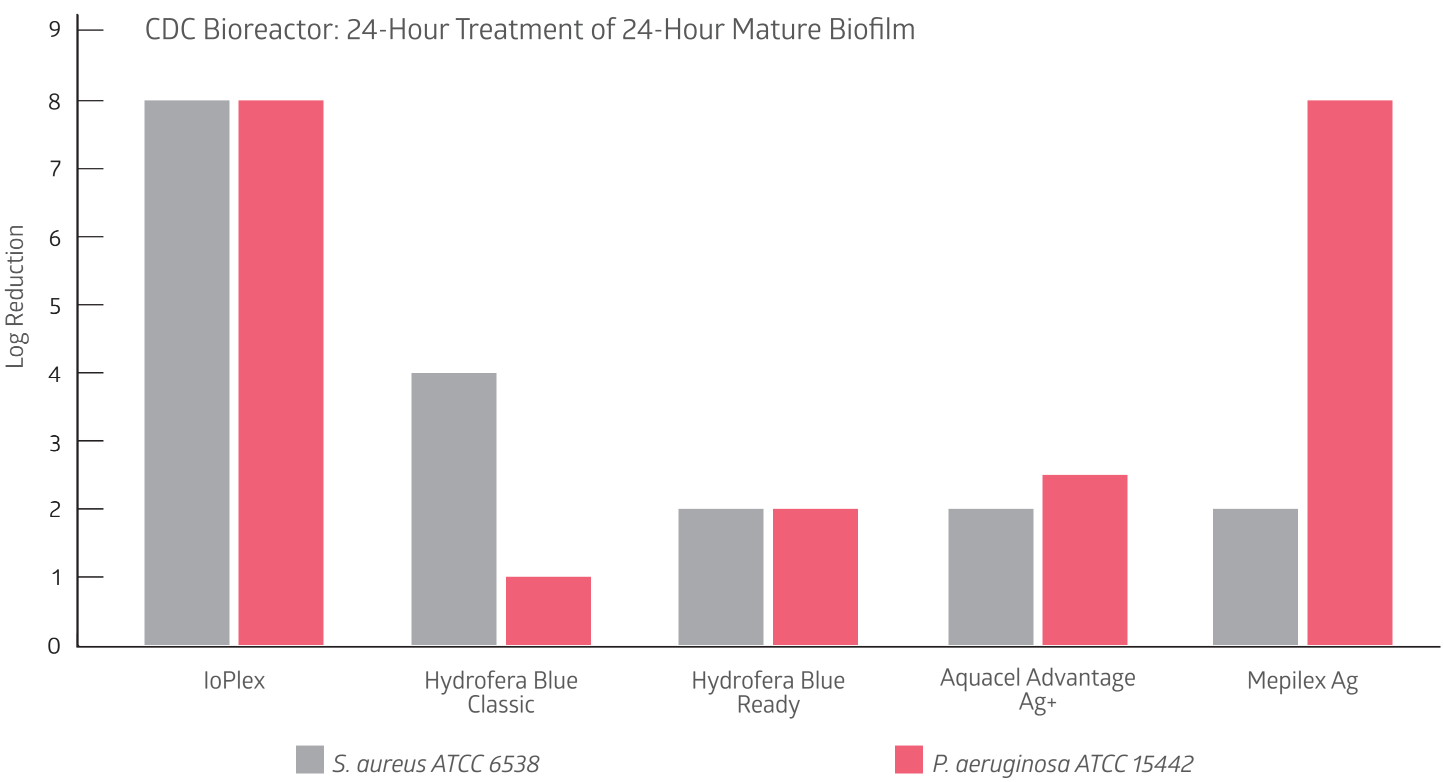
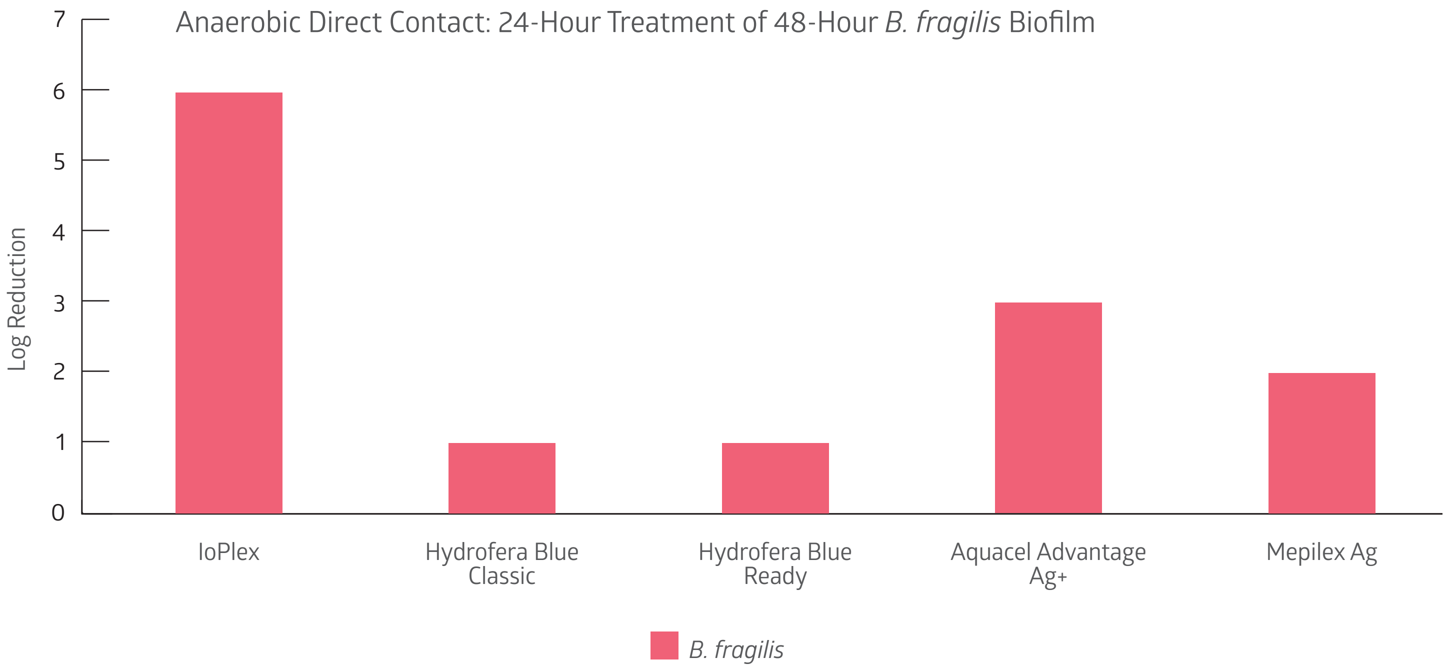


Figure 3: In Vitro Anaerobic Direct Contact Biofilm



Conclusion

In the United States, chronic wounds affect approximately 6.5 million patients, and the number is increasing with the aging population.[22] These wounds are stalled in the inflammatory phase of wound healing and cannot progress. Over 90% of chronic wounds contain biofilm, which is resistant to most antibiotics and many current antibacterial therapies. Managing biofilm poses a challenge, so a range of therapies has been tested in different biofilm models. Iodine dressings have demonstrated significant reduction in biofilm levels in a number of in vitro studies and have consistently outperformed other antibacterial dressings, including silver-based technologies in these studies. IoPlex, a controlled release iodine dressing, has potent activity against mature *S. aureus* and *P. aeruginosa* biofilms in vitro. These results suggest the controlled release of iodine in IoPlex may be effective for managing biofilm in the wound. The clinical implications of these findings have yet to be determined.

References

1. Sanford JA, Gallo, RL. Functions of the skin microbiota in health and disease. Semin. Immunol. 2013; 25: 370–377.

2. International Wound Infection Institute. Wound Infection in Clinical Practice: Principles of Best Practice. International Consensus Update 2016.

3. Guo S, Dipietro LA. Factors affecting wound healing. J. Dent. Res. 2010; 89: 219–229.

4. Bjarnsholt T, et al. Why chronic wounds will not heal: A novel hypothesis. Wound Repair Regen. 2008; 16: 2–10.

5. James GA, Swogger E, Wolcott R, Pulcini Ed, et al. Biofilms in chronic wounds. Wound Repair Regen. 2008; 16(1):37–44.

6. Attinger C and Wolcott R. Clinically addressing biofilm in chronic wounds. Advances in Wound Care. 2012;1(3):127-132.

7. Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nusgart M, Cartwright D. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. Value Health. 2018 Jan;21(1):27-32. doi: 10.1016/j.jval.2017.07.007. Epub 2017 Sep 19.

8. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance [published correction appears in Clin Microbiol Rev 2001 Jan;14(1):227]. Clin Microbiol Rev. 1999;12(1):147-179. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88911/

9. Sibbald RG, Leaper DJ, Queen D. Iodine made easy. Wounds International. 2011;2(20):s1-s6.

10. Wolcott RD, et al. Analysis of the chronic wound microbiota of 2,963 patients by 16S rDNA pyrosequencing. Wound Repair Regen. 2016; 24: 163–174.

11. Kalan L, Grice EA. Fungi in the Wound Microbiome. Adv. Wound Care. 2018; 7: 247–255.

12. Dowd S E, et al. Survey of fungi and yeast in polymicrobial infections in chronic wounds. J. Wound Care. 2014; 20: 40–47.

13. Thorn RM, Austin AJ, Greenman J, Wilkins JP, Davis PJ. In vitro comparison of antimicrobial activity of iodine and silver dressings against biofilms. J Wound Care. 2009 Aug;18(8):343-6.

14. Hill KE, Malic S, McKee R, Rennison T, Harding KG, Williams DW, Thomas DW. An in vitro model of chronic wound biofilms to test wound dressings and assess antimicrobial susceptibilities. J Antimicrob Chemother. 2010 Jun;65(6):1195-206. doi: 10.1093/jac/dkq105. Epub 2010 Apr 8.

15. Phillips PL, Yang Q, Sampson E, Schultz G. Effects of Antimicrobial Agents on an In Vitro Biofilm Model of Skin Wounds. Advances in Wound Care. 2010; 1:299-304.

16. Phillips PL, Yang Q, Davis S, Sampson EM, Azeke JI, Hamad A, Schultz GS. Antimicrobial dressing efficacy against mature Pseudomonas aeruginosa biofilm on porcine skin explants. Int Wound J. 2015 Aug;12(4):469-83. doi: 10.1111/iwj.12142. Epub 2013 Sep 13.

17. Schwarzer S, James GA, Goeres D, Bjarnsholt T, Vickery K, Percival SL, Stoodley P, Schultz G, Jensen SO, Malone M. The efficacy of topical agents used in wounds for managing chronic biofilm infections: A systematic review. J Infect. 2019 Dec 31. pii: S0163-4453(19)30389-5. doi: 10.1016/j.jinf.2019.12.017. [Epub ahead of print]

18. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG. Antibiotics and antiseptics for venous leg ulcers (Review). Cochrane Library. 2010; 10.

19. Data on file.

20. Data on file.

21. Data on file.

22. Sen CK, et al. Human skin wounds: A major and snowballing threat to public health and the economy: Perspective article. Wound Repair Regen. 2009; 17: 763–71.

Medline Industries, Inc.
Three Lakes Drive, Northfield, IL 60093
Medline United States | 1-800-MEDLINE (633-5463)
medline.com | info@medline.com

Medline Canada
1-800-268-2848 | medline.ca | canada@medline.com
Medline México
01-800-831-0898 | medlinemexico.com | mexico@medline.com