Iodine's Impact on Biofilm: Findings of an Expert Panel

Skin Health

"A review of iodine-based compounds, with a focus on biofilms: results of an expert panel" is a clinical review published in *The Journal of Wound Care*. In this clinical review, Drs. Randall D Cook, Gregory S Schultz, Randall G Wolcott, and other wound care experts review the benefits of iodine-based dressings in the management of biofilms.

The presence of biofilm, a layer that covers a wound bed and encases bacterial micro-colonies, contributes to chronic inflammation in at least 60% of all patients with a chronic wound infection.[1, 2] The chemical iodine has been shown to be effective in disrupting biofilm through its multiple diverse mechanisms of action and through its ability to reduce a broad spectrum of bacterial species.

Iodine can be bound to a molecule to create a complex called an iodophor, which facilitates the release of iodine in a controlled manner. In iodophor wound dressings, free iodine is released into the dressing. The release of free iodine creates an equilibrium between the wound dressing and the wound bed. "Slow release" iodophor formulations release iodine in a slow and controlled manner to sustain antibacterial activity over a 3 day period. The controlled release of free iodine in slow release iodophor formulations also reduces cytotoxicity.

Iodophor wound dressings are highly effective in managing both acute and chronic wounds. The clinical review examines several studies that show that iodophor dressings have a broad spectrum of activity against multiple organisms and are rapidly effective in penetrating and managing biofilm.*

Medline's IoPlex® is an absorptive polyvinyl alcohol based foam dressing that is complexed with iodine. IoPlex is a slow release iodophor dressing that minimizes cytotoxicity and includes a visual indicator for dressing change by changing from black to white when the dressing's iodine supply is depleted. As detailed in the clinical review, *in vitro* data shows that IoPlex demonstrates strong antibacterial activity and excellent biofilm control. IoPlex can be used in multiple types of wounds including infected wounds, ulcers (diabetic, pressure, arterial, venous), traumatic wounds, surgical wounds, and burns.

IoPlex Indications for Use

IoPlex Iodophor Foam Dressing is indicated for use in cleaning wet ulcers and wounds, including diabetic ulcers, pressure ulcers, arterial ulcers, venous stasis ulcers, and infected traumatic or surgical wounds and burns.

IoPlex Contraindications

IoPlex contains iodine and should not be used in patients with suspected iodine sensitivity. IoPlex is contraindicated in patients with a history of Graves disease, Hashimoto's thyroiditis, or goiter. Patients with a thyroid disorder history are more susceptible to alterations in thyroid metabolism with chronic iodine therapy. IoPlex should not be used in pregnant or lactating women.

See packaging for more information.

* Disclaimer: Not all iodophor dressing studies referenced in "A review of iodine-based compounds, with a focus on biofilms: results of an expert panel" apply to Medline's IoPlex® wound dressing.

References: 1. Wolcott RD, Rhoads DD, Bennett ME, et al. Chronic wounds and the medical biofilm paradigm. *J Wound Care* 2010;19(2):45-6, 48-50, 52-3. doi:10.12968/jowc.2010.19.2.46966. **2.** Wolcott RD, Rhoads DD, Dowd SE. Biofilms and chronic wound inflammation. J Wound Care 2008;17(8):333-41. doi: 10.12968/jowc.2008.17.8.30796.

Medline Industries, Inc. Three Lakes Drive, Northfield, IL 60093 | 1-800-MEDLINE (633-5463)

A review of iodine-based compounds, with a focus on biofilms: results of an expert panel

Abstract: Biofilms play a central role in the chronicity of non-healing lesions such as venous leg ulcers and diabetic foot ulcers. Therefore, biofilm management and treatment is now considered an essential part of wound care. Many antimicrobial treatments, whether topical or systemic, have been shown to have limited efficacy in the treatment of biofilm phenotypes. The antimicrobial properties of iodine compounds rely on multiple and diverse interactions to exert their effects on microorganisms. An expert panel, held in Las Vegas during the autumn Symposium on Advanced Wound Care meeting in 2018, discussed these properties, with the focus on iodine and iodophors and their effects on biofilm prevention and treatment.
Declaration of interest: Panel members were paid by MedLine Industries for their participation in the expert panel discussion.The corresponding author was paid for writing the manuscript.

biofilms • hard-to-heal wounds • antimicrobials • iodine • iodophors • dressings

Whether defined as skin ulcers or hard-to-heal (also know as chronic),[1] wounds such as venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) are a major burden to patients and to society, with an estimated prevalence of 1% in the general population and as high as 4% in people over 80 years old.[2] From a health-economics point of view, 1% percent of the US budget spent on healthcare is designated to the treatment of VLUs alone.[2] Other sources estimated in 2012 that the annual cost of care in the US for all skin ulcers combined was approximately $25 billion, which translates to a median cost of $3927 per wound.[3] Margolis et al. estimated that the average cost of total US Medicare reimbursement in 2011 was about $33,000 per year for each patient with a DFU.[4]

Much of these costs are directly attributable to the large number of visits to a healthcare provider: it typically takes a long time for these wounds to heal, if they heal at all.[4] Chronicity is caused and sustained primarily by a series of intrinsic factors, which include an imbalance between the overexpression of certain proinflammatory cytokines and metalloproteinases, and the relative downregulation of tissue inhibitors of metalloproteinases.[5] With regard to chronicity, bioburden and infection also play a major role. In particular, the development and presence of biofilm is important. Some consider biofilms an extrinsic contribution to poor healing trends, while others consider the development and presence of a biofilm to be intrinsic.[6] A biofilm is thought to produce destructive enzymes and toxins that contribute to the chronic inflammatory state within the wound.[6] Thus, the existence of a biofilm is one of the main contributors to chronicity.[7–9]

The main characteristic of a hard-to-heal wound is that the healing progress is stalled in 'breakdown mode'. Acute wounds have a more 'healthy', balanced profile with regard to proteases, protease inhibitors, and the different cytokines, which is among the reasons why these wounds generally heal well, without stalling in the healing process.

The scope of the TIME and DIME mnemonics[10–12] provide guidelines on how to treat ulcers. They attempt to comprehensively include all aspects of wound bed preparation that are necessary for healing, including the viability of the tissue in the wound bed, the presence or absence of infection and inflammation, moisture balance, the quality of the wound edges and (the need for) debridement. Biofilm is difficult to treat clinically and has been shown to contribute significantly to wound inflammation.[13,14,15] Numerous treatment options exist, including debridement and the use of antimicrobial agents. The role of antimicrobial agents, either topical or systemic, is sometimes debated. Many, if not most, antimicrobial products have limited efficacy in getting rid of a biofilm since they may not reach or penetrate the exopolymeric matrix, which is a core part of the biofilm construct.

Iodine-containing products, in various molecular compounds and delivery vehicles, have long been used as antimicrobial agents. In 2018, a formal panel of

Randall D Wolcott,[1] MD, Medical Director, **Randall G Cook**,[2] MD, Medical Director, **Eric Johnson**,[3] MD, Medical Director, **Curtis E Jones**,[4] RPh, PhD, Dean and Professor, **John P Kennedy**,[4] RPh, PhD, Research Professor, **Richard Simman**,[5] MD, Director of the Wound Care Program, **Kevin Woo**,[6] PhD RN NSWOC WOCC(C), Associate Professor, **Dot Weir**,[7] RN, CWON, CWS, Professor of Nursing, **Gregory Schultz**,[8] PhD, Professor, ***Michel HE Hermans**,[9] MD, President
***Corresponding author e-mail:** mhermans@hermans-hci.com
1 Southwest Regional Wound Care Center, Lubbock, TX, US. **2** Jackson Wound and Hyperbaric Medicine Center, Montgomery, AL, US. **3** Bozeman Deaconess Wound and Hyperbaric Center, Driggs, ID, US. **4** South University School of Pharmacy, Savannah, GA, US. **5** Jobst Vascular ProMedica, Toledo, OH, US. **6** Queen's School of Nursing, Kingston, ON, Canada. **7** Catholic Health Advanced Wound Healing Centers, Cheektowaga, NY, US. **8** Institute for Wound Research to Study Molecular and Cellular Regulation of Healing, University of Florida, Gainesville, FL, US. **9** Hermans Consulting Inc., Doral, FL, US.

clinicians and researchers was organised during the fall meeting of the Symposium of Advanced Wound Care in Las Vegas, to discuss the antimicrobial properties of different iodine compounds, particularly in regard to the prevention and management of biofilms. All authors were participants in the expert panel, which was supported by Medline Industries, Inc.

Iodine

Chemistry

The element iodine was discovered in 1881 by the French chemist Barnard Courtois, who identified it while extracting compounds from seaweed. Today, iodine is primarily derived from sodium iodate ($NaIO_3$) and sodium periodate ($NaIO_4$), deposits of which are found in Chile and Bolivia.[16] The name is derived from the Greek 'iodes' meaning violet.

Iodine (symbol: I, atomic number 53) is a member of the halogen family, the 17th group of the periodic table, as are fluorine, chlorine, and bromine (the radioactive elements astatine, one of the rarest on earth, and tennessine, an artificial element, are also placed in this group; they have a very short half-life and their chemical properties are not well understood). Iodine exists in a number of different ionic forms as well as isotopes, I^{127} being the sole stable isotope. All halogens are characterised by seven valence electrons in their outer shell. Lacking one electron from a full set of eight valence electrons, they are highly reactive, readily forming bonds and scavenging the 'final' electron from neighboring atoms to fill the outer electron shell. In this manner, they attain a full and stable set of eight electrons resulting in a net negative charge of '–1' for the iodide ion. Iodide (I^-) is one of the largest monatomic anions and, partly because of its large size, iodide ions normally form bonds with other elements that are relatively weak.[17] Most iodide salts are soluble in water, but often less so than the related chlorides and bromides.

Biological mode of action of iodine.

Iodine has been used as an antimicrobial agent for more than a century.[18] The microbicidal mode of action of iodine is multifaceted, leveraging many diverse mechanisms, which contribute to the broad spectrum of activity. Iodine interacts or inhibits a number of cellular structures and cellular mechanisms, present in many different types of organisms;[19–23] amino acids and fatty acids in the bacterial membrane are oxidised (give up an electron to iodine atoms), as are cellular nucleotides. Iodine also reacts with enzymes of the cytosol involved in the respiratory chain, leading to denaturation as well as deactivation.[24] In addition to its antimicrobial properties, iodine has also been shown to have certain anti-inflammatory effects.[25] Furthermore, to date, in numerous *in vitro* experiments, no microbial resistance has been demonstrated for iodine.[20,26–29]

Vermeulen et al. published a systematic review of 27 randomised clinical trials, with different indications such as burns, pressure ulcers (PU) and split-thickness skin grafts. The authors assessed the outcomes of the articles on adverse effects, bacterial count and wound healing and concluded that iodine does not lead to lengthening of the healing process, and that adverse effects, including those on functions of the thyroid, are very rare.[30]

Formulations and compounds

The original therapeutic formulation of iodine was 'iodine tincture', by definition a medicine made by dissolving a compound in alcohol. Iodine tincture was shown to be effective (although for a short period and not with biofilm phenotypes) as an antibacterial agent for acute wound and skin indications. In pure aqueous solutions of iodine, at least seven different ions or molecules are present,[31] with molecular iodine (I_2), hydrated iodine cation (H_2OI^+) and hypoiodous acid (HOI) having the most accepted antimicrobial properties.[32] The concentration of the iodine cation in aqueous solution, however, is too low to play a significant role in the disinfection process.[33] As with most tinctures (alcohol based), treatment of breached skin with iodine tincture is extremely painful.[21,34,35]

An iodophor is a special type of compound containing iodine temporarily bound to a carrier molecule (typically a polymer). This temporary bond is called a 'complex', or charge transfer complex, which chemically defines an iodophor. Under the right conditions, the iodine will dissociate from the carrier molecule and release free iodine.

Iodophors were developed in an attempt to overcome some of the deficiencies of hydroalcoholic tinctures. They are made from different carriers (complexing agents). The complexing agent used to produce the iodine complex gives the resulting iodophor different physical properties (liquid, semisolid, solid), and hence different uses. These include increasing the solubility and the carrying capacity of iodine, providing a sustained-release reservoir and speeding up or slowing down the release of iodine, and/or reducing the equilibrium concentration of free molecular iodine.[31]

There are three different types of iodophors available in the US as wound dressings;[36] they are based on povidone (liquid), cadexomer (semi-solid), and polyvinyl alcohol (PVA)-based foam (solid) as carriers. Povidone-iodine is a liquid chemical complex of povidone (a generic name for the complexed polymer polyvinyl pyrrolidone), hydrogen iodide and elemental iodine. It contains 9–12% weight for weight (w/w) iodine. It is one of the few topical antimicrobial agents that demonstrated efficacy against amoebic cysts, bacteria, fungi, spores, several viruses and protozoa.[19,20,35,37]

Cadexomer iodine is an iodophor produced by the reaction of dextrin with epichlorohydrin and iodine. The resulting compound is a modified polymer that contains 0.9% (w/w) iodine. It is a paste-like semi-solid when compounded with other excipients.

A newer iodophor consists of an absorptive PVA-based foam dressing (IoPlex, Medline Industries Inc., US), which

is complexed with iodine and contains 8% iodine (w/w). The exact chemical structure of this solid-state iodophor has not yet been fully elucidated. The dressing is specifically indicated for use on infected wounds, an indication of remarkably few advanced dressings.

Many iodophors have controlled properties of iodine release, but specific mechanisms for these slow-release complexes are not well understood. As previously presented, it is proposed that the polymers form noncovalent associations with iodine molecules in a complex. Under the proper conditions, iodine is liberated locally for presentation to the wound bed at a rate that corresponds to the specific complex (iodophor) employed.

An iodophor releases free iodine within the dressing; the microbicidal activity of iodophors is determined largely by their galenic form. Iodophors create an equilibrium within the dressing with the wound fluid. Therefore, more (free) iodine is released from the iodophor as iodine is 'consumed' by microorganisms that enter the dressing.[19,33,38,39] In this manner, the iodine release is 'on demand'. The quantitative release properties are specific to the iodophor compound, however, and to the corresponding formulation in which the iodophor resides. Slow-release iodophor formulations are intended, at least in part, to reduce cytotoxicity and the chance of 'dose dumping' of the active iodine.[40] The equilibrium using this 'iodine delivery system' significantly improves both tolerability and safety when compared with other formulations containing elemental iodine or faster-releasing iodophors,[35] leading to decreased toxicity.[21] Iodophors also diminish the unpleasant odour, irritation, tissue staining and corrosion associated with iodine tinctures.[41]

In an *in vitro* experiment in which Franz diffusion static cells with human skin were used, iodine absorption through the skin was studied. The experiment showed that povidone-iodine can permeate through skin in relevant amounts.[42] In burn studies in humans it was shown, however, that although iodine released from iodophors is absorbed through wounded skin, the actual amount depends on the type of iodophor.[43] Thus, systemic complications are possible, particularly when the agent is used on large wounds, such as large surface area burns, but such complications remain rare.[25,43,44] Data indicate that even in extensive burns, a cause-and-effect relationship between iodine absorption and complications such as hypernatraemia and metabolic acidosis could not be established.[45] Although iodine sensitisation occurs, the actual sensitisation rate is estimated to be about 0.7%.[46]

Iodophors have been shown to have a high level of efficacy in many different types of wounds,[47-49] and multiple studies indicate enhanced wound healing when slow-release iodophors are used.[49,50]

(Note: a different iodine delivery system exists, which consists of an iodine-containing dressing in combination with an enzyme that provides oxygen to the wound. This product was tested with good clinical results[51] but it is not available in the US).

Cytotoxicity

Iodine tincture has demonstrated a dose-dependent cytotoxicity (for human keratinocytes and fibroblasts).[52-54] Van Meurs et al.,[55] in an *in vitro* setting, exposed *Staphylococcus aureus* and *Staphylococcus epidermidis* as well as human fibroblasts and mesenchymal stromal cells to polyhexanide, hydrogen peroxide, octenidine dihydrochloride, povidone-iodine and chlorhexidine digluconate at various dilutions for two minutes. The cytotoxicity of iodine was shown to be very low when compared with the other topical agents.[55,56]

Bigliardi et al.[25] undertook an extensive literature review and concluded that the combination of clinical safety (with regard to toxicity to mammalian cells) and efficacy (as an antimicrobial agent) makes iodophors good candidates for the successful treatment of acute and hard-to-heal wounds.[25] Cooper, in a separate but similar literature study, came to a similar conclusion.[57]

Biofilms

It is safe to assume that virtually all wounds have a certain level of bacterial contamination. Although the presence of planktonic bacteria does not necessarily interfere with wound healing, the formation and presence of a biofilm certainly does.[58] Biofilms are omnipresent in non-healing ulcers[59] (hard-to-heal wounds)—it is conservatively estimated that in at least 60% of all patients with a hard-to-heal wound infection, biofilms play an essential role in such chronicity.[8,9] Once the host defense is breached, planktonic bacteria enter the wound where the tissues have reduced defenses to mitigate attachment. Therefore, with time and opportunity, the bacteria attach themselves to an (exposed) host surface, naturally adopting the biofilm phenotype; when these bacteria are not rapidly cleared by the host immune system the formation of micro-colonies is initiated.[60] The genetic expression of the bacteria in the colonies is changed and this maturing biofilm begins exuding an exopolymeric matrix in which they encase themselves. In doing so, the microbial communities fortify themselves against the host immune system. 'Quorum-sensing' is a form of chemical communication used to determine when a sufficient number of bacteria (a quorum) is present, which triggers the shift in expression and a change to the nascent cells representing a biofilm.[14,61] The presence of the biofilm attracts excess neutrophils, accompanied by proinflammatory cytokines and proteases. This initiates (or continues/intensifies) the (hyper) inflammatory wound environment which is, in fact, one of the primary reasons for chronicity in wounds.[5,15,59,62,63] The influence of biofilm on wound healing was confirmed *in vivo* by animal testing using a rabbit ear biofilm model; the presence of biofilm was shown to extend the chronicity of these non-healing wounds.[7] These data were confirmed in experiments with mouse skin wounds where planktonic *Staphylococcus aureus* bacteria inoculated into acute wound beds formed biofilms that impaired healing compared with uninoculated control

wounds, and wounds inoculated with planktonic *Staphylococcus aureus* bacteria that were prevented from forming biofilms by treatment with the quorum system inhibitor.[64]

Biofilms and iodine

In a number of *in vitro* and *ex vivo* studies, iodophors have been shown to be able to penetrate and disrupt biofilms.[25,65,66] Philips et al.[67] tested several antimicrobial agents (iodine, silver, polyhexamethylene biguanide, honey and ethanol) and a number of moisture-retaining dressings (sodium carboxymethyl cellulose fibre, calcium alginate fibre, cotton gauze and cadexomer beads) in an explant porcine skin biofilm model at different levels of maturity of the biofilm (0–3 days). This model uses tryptic soy agar and is very well established and recognised for this type of study.[66,67] They showed that cadexomer iodine dressings (slow-releasing iodophor) and a time-release silver gel were most effective in reducing mature biofilms (between 5 and 7 logs) with a single exposure. The remaining challenge materials had significantly less impact, reducing biofilm between 0.3 and 2 logs within 24–72 hours.[67]

In a different *in vitro* experiment, three different iodine-releasing test dressings were placed on cellulose filter discs, which were inoculated with different microorganisms (*Fusobacterium nucleatum*, *Bacteroides fragilis*, *Pseudomonas aeruginosa*, *Propionibacterium acnes*, *Staphylococcus epidermidis*, meticillin-resistant *Staphylococcus aureus* and *Candida albicans*). Kill curves were created from determinations of the numbers of survivors (log colony-forming units (CFU) per disc) over time. The authors concluded that the dressings are broad-spectrum in activity and are rapidly effective, including against antibiotic-resistant organisms, yeasts and anaerobes.[68]

Hill et al. used *in vitro*-developed biofilms to assess the susceptibility of bacteria using light- and scanning electron microscopy. Their experiment showed that ciprofloxacin or flucloxacillin, even at concentrations equivalent to twice the observed peak serum levels, did not disrupt mixed *Staphylococcus/Pseudomonas* biofilms, while a povidone-iodine dressing (1%) rapidly disrupted biofilms established for seven days and was more efficacious than the silver dressings under study.[65]

Using a mathematical model, Gogan et al. demonstrated that slow release of antimicrobial agents in low concentrations is more effective than short-term exposure with a high concentration of the same compound.[69] Indeed, very reactive agents such as hypochlorous acid react so aggressively with wound compounds that they are fully expended before reaching the deeper layers of the biofilm,[66] a phenomenon termed the 'reactive diffusion problem'. Thus, such rapid release agents must be reapplied frequently to reach a high level of efficacy.[66] Indeed, in one study cadexomer iodine efficacy was found to require two to three dressing changes per day to have an optimal effect.[70] Perhaps these findings may be viewed as only logical, considering the time dependence of many antimicrobial agents.

The support for slow-release compounds is confirmed by a Cochrane analysis on the efficacy of antibiotics and antiseptics for the management of VLUs.[29] The authors concluded that with regard to the healing of venous leg ulcers, 'in terms of topical preparations, some evidence supports the use of cadexomer iodine'. They also stated that the same type of evidence does not exist for compounds such as chlorhexidine, and honey-, silver-, and peroxide-based compounds.[29]

In vitro experiments on the PVA-based foam iodophor have shown that the dressing releases iodine slowly and in a controlled manner. Similar to other iodophors, the compound has a relatively low level of toxicity to mammalian cells.[71] *In vitro* data indicate that this dressing has very good antibacterial activity. Using an established *in vitro* biofilm model with clinical strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*, this iodophor demonstrated excellent biofilm control with 8 log reductions for up to three days under a broad range of microbial diversity, exudate flow rates and durations.[71] The dressing is easy to use, does not stain and has good tensile strength. In addition, the dressing's colour changes from black to white on the depletion of iodine supply, as a visual indication of the need to change.

Clinical implications

The presence of a biofilm is a major barrier to the healing of skin ulcers and, therefore, on the quality of life[72] of patients with hard-to-heal wounds. The economic burden to society is also significant.[59] Therefore, early intervention, aimed at management of wound biofilm by removal (debridement) and adjunct antimicrobial treatment is an established essential strategy to positively impact the healing trajectory.[73]

Regular mechanical debridement has been shown to probably be the most effective way to reach the goal of removal of the biofilm[58,61] as well as other benefits. For various practice and practical limitations, however, debridement is not always accessible. Thus, a reliable antimicrobial adjunct or follow-up therapy is a welcome and necessary tool in many clinical settings to further manage wound biofilm or prevent its reformation.[58]

Although certain compounds, such as specific antimicrobial peptides, may hold some promise,[74,75] many options have shown limited efficacy to date in wound care,[65,76] at least in part due to a combination of poor penetration of the exopolymeric matrix and bacterial biofilm tolerance.

The ideal antimicrobial should combine a range of properties, including being active against a broad series of microorganisms, having a low potential for (acquired) resistance and being able to penetrate into eschar/necrosis and biofilm.[35,77,78] Such an antimicrobial dressing should also support additional aspects of wound healing (including suppression or correction of hyperinflammation), have a low toxicity level, and be well tolerated (i.e. not painful) and affordable.[35,77]

A limited number of topical antimicrobial agents offer the potential to provide such ideals. However, among these, iodophors have an admirable success rate in part due to the multiple mechanisms of action on microbes, even in the biofilm phenotype. Iodine provides a broad species spectrum, while slow release iodophors provide the prolonged exposure via sustained release of iodine to be effective on both planktonic and biofilm phenotypes.

Guidelines by the European Congress of Clinical Microbiology and Infectious Diseases in 2015 have provided strategies for the collection of clinical samples, and the reliable identification of a biofilm.[79] With regard to actual treatment, a new, step-down approach has been proposed by Schultz et al.[73] Part of this strategy is guided by the earlier findings, published by the International Wound Infection Institute (IWII)[80] which met in 2016 to issue recommendations on the use of bacterial management products (for planktonic and biofilm bacteria). IWII concluded that slow-release iodine use is recommended as a first line therapy for bacterial management in wounds.[80]

The step-up/step-down approach takes a holistic approach and includes aspects of wound healing in the broadest sense, including adjunct (but very important) therapies such as offloading of DFUs and PUs, and compression for patients with VLUs. With this approach, therapy starts aggressively and, when possible, over time becomes less aggressive, deescalating as the wound improves.[73] The step-down approach focuses on the prevention and treatment of biofilm as one of the essential steps in healing. The use of iodine is consistent with this methodology of treatment as a general consensus exists that iodine is a powerful and aggressive antimicrobial agent.

Conclusion

Management of wound biofilm is essential for healing of hard-to-heal wounds. A combination therapy of debridement, topical antibacterial therapy and, depending on the type of wound, adjunct therapies, offers the highest level of consistent, reproducible, success. Controlled-release iodophors, with their wide antimicrobial spectrum, confirmed long-lasting efficacy, and limited adverse reactions, are appropriate agents for aggressively and reliably controlling biofilms and realigning wounds to a positive healing trajectory. **JWC**

References

1 Hermans MH. Wounds and ulcers: back to the old nomenclature. Wounds 2010; 22(11):289–293
2 Böhler K. [Venous ulcer]. Wien Med Wochenschr 2016; 166(9–10):287–292. https://doi.org/10.1007/s10354-016-0487-5
3 Fife CE, Carter MJ. Wound care outcomes and associated cost among patients treated in US outpatient wound centers: data from the US Wound Registry. Wounds 2012; 24(1):10–17
4 Margolis DJ, Malay DS, Hoffstad OJ et al. Economic burden of diabetic foot ulcers and amputations: data points #3. Data Points Publication Series. Agency for Healthcare Research and Quality 2011
5 Loo WT, Sasano H, Chow LW. Pro-inflammatory cytokine, matrix metalloproteinases and TIMP-1 are involved in wound healing after mastectomy in invasive breast cancer patients. Biomed Pharmacother 2007; 61(9):548–552. https://doi.org/10.1016/j.biopha.2007.08.012
6 Rajpaul K. Biofilm in wound care. Br J Community Nurs 2015; 20(Suppl 3 Wound Care):S6–S11. https://doi.org/10.12968/bjcn.2015.20.sup3.s6
7 Seth AK, Geringer MR, Gurjala AN et al. Treatment of Pseudomonas aeruginosa biofilm-infected wounds with clinical wound care strategies: a quantitative study using an in vivo rabbit ear model. Plast Reconstr Surg 2012 Fb; 129(2):262e–274e. https://doi.org/10.1097/PRS.0b013e31823aeb3b
8 Wolcott RD, Rhoads DD, Bennett ME et al. Chronic wounds and the medical biofilm paradigm. J Wound Care 2010; 19(2):45–53. https://doi.org/10.12968/jowc.2010.19.2.46966
9 Wolcott RD, Rhoads DD, Dowd SE. Biofilms and chronic wound inflammation. J Wound Care 2008; 17(8):333–341. https://doi.org/10.12968/jowc.2008.17.8.30796
10 Leaper DJ, Schultz G, Carville K et al. Extending the TIME concept: what have we learned in the past 10 years?*. Int Wound J 2012; 9 (Suppl 2):1–19. https://doi.org/10.1111/j.1742-481X.2012.01097.x
11 Schultz GS, Barillo DJ, Mozingo DW, Chin GA; Wound Bed Advisory Board Members. Wound bed preparation and a brief history of TIME. Int Wound J 2004; 1(1):19–32. https://doi.org/10.1111/j.1742-481x.2004.00008.x
12 Manna B, Morrison CA. Wound Debridement. StatPearls. Treasure Island (FL) 2019
13 Gurjala AN, Geringer MR, Seth AK et al. Development of a novel, highly quantitative in vivo model for the study of biofilm-impaired cutaneous wound healing. Wound Repair Regen 2011; 19(3):400–410. https://doi.org/10.1111/j.1524-475X.2011.00690.x
14 Clinton A, Carter T. Chronic wound biofilms: pathogenesis and potential therapies. Lab Med 2015; 46(4):277–284. https://doi.org/10.1309/LMBNSWKUI4JPN7SO
15 Percival SL, Hill KE, Williams DW et al. A review of the scientific evidence for biofilms in wounds. Wound Repair Regen 2012; 20(5):647–657. https://doi.org/10.1111/j.1524-475X.2012.00836.x
16 Fassiadis N, Kapetanakis E, Law N. Etiology of leg ulcers, healing and recurrence rates in octo- and nonagenarians. Int Angiol 2002; 21(2):193–195
17 PubChem. Iodide ion. https://pubchem.ncbi.nlm.nih.gov/compound/30165 (accessed 16 June 2020)
18 Schofield M. Chapters in iodine's history. Pharm J 1947; 104(4343):68
19 Fleischer W, Reimer K. Povidone-iodine in antisepsis—state of the art. Dermatology 1997; 195 suppl 2:3–9. https://doi.org/10.1159/000246022
20 Durani P, Leaper D. Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation. Int Wound J 2008; 5(3):376-387. https://doi.org/10.1111/j.1742-481x.2007.00405.x
21 Leaper DJ, Durani P. Topical antimicrobial therapy of chronic wounds healing by secondary intention using iodine products. Int Wound J 2008; 5(2):361–368. https://doi.org/10.1111/j.1742-481X.2007.00406.x
22 Mangram AJ, Horan TC, Pearson ML et al.; Hospital Infection Control Practices Advisory Committee. Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol 1999; 20(4):247–280. https://doi.org/10.1086/501620
23 Schreier H, Erdos G, Reimer K et al. Molecular effects of povidone-iodine on relevant microorganisms: an electron-microscopic and biochemical study. Dermatology 1997; 195(sup 2):111–116. https://doi.org/10.1159/000246043
24 Kanagalingam J, Feliciano R, Hah JH et al. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. Int J Clin Pract 2015; 69(11):1247–1256. https://doi.org/10.1111/ijcp.12707
25 Bigliardi PL, Alsagoff SA, El-Kafrawi HY et al. Povidone iodine in wound healing: a review of current concepts and practices. Int J Surg 2017; 44:260–268. https://doi.org/10.1016/j.ijsu.2017.06.073
26 Fischer J, Fegelman E. Johannigman J. Surgical complications. In: Schwartz S, Shires G, Spencer F et al., eds. Principles of surgery. 7th edn. McGraw-Hill 1999:601–665
27 Kunisada T, Yamada K, Oda S, Hara O. Investigation on the efficacy of povidone-iodine against antiseptic-resistant species. Dermatology 1997; 195(sup 2):14–18. https://doi.org/10.1159/000246025
28 Lachapelle JM. A comparison of the irritant and allergenic properties of antiseptics. Eur J Dermatol 2014; 24(1):3–9. https://doi.org/10.1684/ejd.2013.2198
29 O'Meara S, Al-Kurdi D, Ologun Y et al. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev 2014; (1):CD003557. https://doi.org/10.1002/14651858.CD003557.pub5

Reflective questions

- How are biofilm bacteria different from planktonic bacteria?
- What is quorum sensing?
- What is the difference between iodine tincture and iodophors?

30 Vermeulen H, Westerbos SJ, Ubbink DT. Benefit and harm of iodine in wound care: a systematic review. J Hosp Infect 2010; 76(3):191–199. https://doi.org/10.1016/j.jhin.2010.04.026
31 Gottardi W. Iodine and iodine compounds. In: Block SS, ed. Disinfection, Preservation and Sterilization. 4th edn. Lea & Febiger 1991:152–165
32 Black AP, Kinman RN, Keirn MA et al. The disinfection of swimming pool waters. I. Comparison of iodine and chlorine as swimming pool disinfectants. Am J Public Health Nations Health 1970; 60(3):535–545. https://doi.org/10.2105/AJPH.60.3.535
33 Gottardi W. The influence of the chemical behaviour of iodine on the germicidal action of disinfectant solutions containing iodine. J Hosp Infect 1985; 6(1 Suppl A):1–11. https://doi.org/10.1016/S0195-6701(85)80040-2
34 Laufman H. Current use of skin and wound cleansers and antiseptics. Am J Surg 1989; 157(3):359–365. https://doi.org/10.1016/0002-9610(89)90570-9
35 Ripa S, Bruno R, Reder R. Clinical applications of povidone-iodine as a topical antimicrobial. In: Paulson DS, ed. Handbook of topical antimicrobials: industrial applications in consumer products and pharmaceuticals. CRC Press, 2002
36 Kestrel Health Information Inc. Antimicrobial dressings. In: Woundsource 2018; Kestrel Health Information Inc, 2018
37 Summa M, Russo D, Penna I et al. A biocompatible sodium alginate/povidone iodine film enhances wound healing. Eur J Pharm Biopharm 2018; 122:17–24. https://doi.org/10.1016/j.ejpb.2017.10.004
38 Rackur H. New aspects of mechanism of action of povidone-iodine. J Hosp Infect 1985; 6(suppl A):13–23
39 Gottardi W, Koller W. The concentration of free iodine in aqueous PVP-iodine containing systems and its variation with temperature. Monatschäfte fur Chemie 1986; (117):1011–1020
40 Kramer SA. Effect of povidone-iodine on wound healing: a review. J Vasc Nurs 1999; 17(1):17–23. https://doi.org/10.1016/S1062-0303(99)90004-3
41 Anderson RL. Iodophor antiseptics: intrinsic microbial contamination with resistant bacteria. Infect Control Hosp Epidemiol 1989; 10(10):443–446. https://doi.org/10.2307/30146832
42 Nesvadbova M, Crosera M, Maina G, Larese Filon F. Povidone iodine skin absorption: An ex-vivo study. Toxicol Lett 2015; 235(3):155–160. https://doi.org/10.1016/j.toxlet.2015.04.004
43 Notea E, Hirshowitz B. Comparison of blood serum iodine levels with use of Iodoplex and povidone iodine ointment. J Trauma Inj Infect Crit Care 1985; 25(3):247–249. https://doi.org/10.1097/00005373-198503000-00015
44 Dela Cruz F, Brown DH, Leikin JB et al. Iodine absorption after topical administration. West J Med 1987; 146(1):43–45
45 Hunt JL, Sato R, Heck EL, Baxter CR. A critical evaluation of povidone-iodine absorption in thermally injured patients. J Trauma Inj Infect Crit Care 1980; 20(2):127–129. https://doi.org/10.1097/00005373-198002000-00004
46 Niedner R. Cytotoxicity and sensitization of povidone-iodine and other frequently used anti-infective agents. Dermatology 1997; 195(sup 2):89–92. https://doi.org/10.1159/000246038
47 Hansson C; Cadexomer Iodine Study Group. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Int J Dermatol 1998; 37(5):390–396. https://doi.org/10.1046/j.1365-4362.1998.00415.x
48 Miller CN, Newall N, Kapp SE et al. A randomized-controlled trial comparing cadexomer iodine and nanocrystalline silver on the healing of leg ulcers. Wound Repair Regen 2010; 18(4):359–367. https://doi.org/10.1111/j.1524-475X.2010.00603.x
49 Ohtani T, Mizuashi M, Ito Y, Aiba S. Cadexomer as well as cadexomer iodine induces the production of proinflammatory cytokines and vascular endothelial growth factor by human macrophages. Exp Dermatol 2007; 16(4):318–323. https://doi.org/10.1111/j.1600-0625.2006.00532.x
50 Drosou A, Falabella A, Kirsner RS. Antiseptics on wounds: an area of controversy. Wounds 2003; 15(5):149–166
51 Thorn RM, Greenman J, Austin AS. An in vitro study of antimicrobial activity and efficacy of iodine-generating hydrogel dressings. J Wound Care 2006; 15(7):305–310. https://doi.org/10.12968/jowc.2006.15.7.26929
52 Fabreguette A, Zhi Hua S, Lasne F, Damour O. [Evaluation of the cytotoxicity of antiseptics used in current practice on cultures of fibroblasts and keratinocytes]. Pathol Biol (Paris) 1994; 42(9):888–892
53. Iwasawa A, Nakamura Y. [Cytotoxic effect and influence of povidone-iodine on wounds in guinea pig]. J Japanese Association Infectious Diseases 2003; 77(11):948–956. https://doi.org/10.11150/kansenshogakuzasshi1970.77.948
54 Teepe RG, Koebrugge EJ, Löwik CW et al. Cytotoxic effects of topical antimicrobial and antiseptic agents on human keratinocytes in vitro. J Trauma 1993; 35(1):8–19. https://doi.org/10.1097/00005373-199307000-00002
55 van Meurs SJ, Gawlitta D, Heemstra KA et al. Selection of an optimal antiseptic solution for intraoperative irrigation: an in vitro study. J Bone Joint Surg Am 2014; 96(4):285–291. https://doi.org/10.2106/JBJS.M.00313
56 Schmidt J, Zyba V, Jung K et al. Effects of octenidine mouth rinse on apoptosis and necrosis of human fibroblasts and epithelial cells – an in vitro study. Drug Chem Toxicol 2018; 41(2):182–187. https://doi.org/10.1080/01480545.2017.1337124
57 Cooper RA. Iodine revisited. Int Wound J 2007; 4(2):124–137. https://doi.org/10.1111/j.1742-481X.2007.00314.x
58 Percival SL, Vuotto C, Donelli G, Lipsky BA. Biofilms and wounds: an identification algorithm and potential treatment options. Adv Wound Care 2015; 4(7):389–397. https://doi.org/10.1089/wound.2014.0574
59 Malone M, Bjarnsholt T, McBain AJ et al. The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. J Wound Care 2017; 26(1):20–25. https://doi.org/10.12968/jowc.2017.26.1.20
60 Harrison-Balestra C, Cazzaniga AL, Davis SC, Mertz PM. A wound-isolated Pseudomonas aeruginosa grows a biofilm in vitro within 10 hours and is visualized by light microscopy. Dermatol Surg 2003; 29(6):631–635
61 Omar A, Wright J, Schultz G et al. Microbial biofilms and chronic wounds. microorganisms 2017; 5(1):9. https://doi.org/10.3390/microorganisms5010009
62. Dobaczewski M, Gonzalez-Quesada C, Frangogiannis NG. The extracellular matrix as a modulator of the inflammatory and reparative response following myocardial infarction. J Mol Cell Cardiol 2010; 48(3):504–511. https://doi.org/10.1016/j.yjmcc.2009.07.015
63 Utz ER, Elster EA, Tadaki DK et al. Metalloproteinase expression is associated with traumatic wound failure. J Surg Res 2010; 159(2):633–639. https://doi.org/10.1016/j.jss.2009.08.021
64 Schierle CF, De la Garza M, Mustoe TA, Galiano RD. Staphylococcal biofilms impair wound healing by delaying reepithelialization in a murine cutaneous wound model. Wound Repair Regen 2009; 17(3):354–359. https://doi.org/10.1111/j.1524-475X.2009.00489.x
65 Hill KE, Malic S, McKee R et al. An in vitro model of chronic wound biofilms to test wound dressings and assess antimicrobial susceptibilities. J Antimicrob Chemother 2010; 65(6):1195–1206. https://doi.org/10.1093/jac/dkq105
66 Johani K, Malone M, Jensen SO et al. Evaluation of short exposure times of antimicrobial wound solutions against microbial biofilms: from in vitro to in vivo. J Antimicrob Chemother 2018;73(2):494–502. https://doi.org/10.1093/jac/dkx391
67 Phillips PL, Yang Q, Davis S et al. Antimicrobial dressing efficacy against mature Pseudomonas aeruginosa biofilm on porcine skin explants. Int Wound J 2015; 12(4):469–483. https://doi.org/10.1111/iwj.12142
68 Thorn RM, Austin AJ, Greenman J et al. In vitro comparison of antimicrobial activity of iodine and silver dressings against biofilms. J Wound Care 2009; 18(8):343–346. https://doi.org/10.12968/jowc.2009.18.8.43635
69 Cogan N, Cortez R, Fauci L. Modeling physiological resistance in bacterial biofilms. Bull Math Biol 2005; 67(4):831–853. https://doi.org/10.1016/j.bulm.2004.11.001
70 Schwartz JA, Lantis JC 2nd, Gendics C et al. A prospective, non comparative, multicenter study to investigate the effect of cadexomer iodine on bioburden load and other wound characteristics in diabetic foot ulcers. Int Wound J 2013; 10(2):193–199. https://doi.org/10.1111/j.1742-481X.2012.01109.x
71 Kennedy JP, Jones CE. Antimicrobial biofilm profiles of a controlled release foam iodophor dressing. Innovations in wound healing. Key West, 2018. Poster and oral presentation at the 'Innovations in wound healing' conference, Key Largo, FL, 7–10 December 2018
72 Woo K, Hill R, LeBlanc K et al. Effect of a surfactant-based gel on patient quality of life. J Wound Care 2018; 27(10):664–678. https://doi.org/10.12968/jowc.2018.27.10.664
73 Schultz G, Bjarnsholt T, James GA et al.; Global Wound Biofilm Expert Panel. Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds. Wound Repair Regen 2017; 25(5):744–757. https://doi.org/10.1111/wrr.12590
74 Jaśkiewicz M, Neubauer D, Kazor K et al. Antimicrobial activity of selected antimicrobial peptides against planktonic culture and biofilm of Acinetobacter baumannii. Probiotics Antimicrob Proteins 2019; 11(1):317-324 https://doi.org/10.1007/s12602-018-9444-5
75 Xie J, Li Y, Li J et al. Potent effects of amino acid scanned antimicrobial peptide Feleucin-K3 analogs against both multidrug-resistant strains and biofilms of Pseudomonas aeruginosa. Amino Acids 2018; 50(10):1471–1483. https://doi.org/10.1007/s00726-018-2625-4
76 Salisbury AM, Woo K, Sarkar S et al. Tolerance of biofilms to antimicrobials and significance to antibiotic resistance in wounds. Surg Technol Int 2018; 33:59–66
77 König B, Reimer K, Fleischer W, König W. Effects of Betaisodona on parameters of host defense. Dermatology 1997; 195(sup 2):42–48. https://doi.org/10.1159/000246029
78 Sakarya S, Gunay N, Karakulak Me t al. Hypochlorous acid: an ideal wound care agent with powerful microbicidal, antibiofilm, and wound healing potency. Wounds 2014; 26(12):342–350
79 Høiby N, Bjarnsholt T, Moser C et al. ESCMID* guideline for the diagnosis and treatment of biofilm infections 2014. Clin Microbiol Infect 2015; 21(Suppl 1):S1–S25. https://doi.org/10.1016/j.cmi.2014.10.024
80 International Wound Infection Institute. Wound infection in clinical practice: international consensus update. Wounds International, 2016