CLINICAL MANAGEMENT extra

Update: Topical Antimicrobial Agents for Chronic Wounds

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GENERAL PURPOSE:

To provide information on the use of topical antimicrobial agents for the treatment of chronic wounds.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After participating in this educational activity, the participant should be better able to:

1. Examine features of wounds and wound healing as well as the purpose of specific antimicrobial agents.

2. Identify potential therapeutic and adverse effects of specific topical antimicrobial agents for the treatment of chronic wounds.

ABSTRACT

Bacteria can delay or prevent healing in the surface compartment of a chronic wound or invade the deep and surrounding structures. This article focuses on the superficial compartment and the appropriate use of topical antimicrobial therapies. The authors have reviewed the published evidence for the last 5 years (2012–2017) and extrapolated findings to clinical practice with critical appraisal and synthesis of the recent literature with expert opinion, patient-centered concerns, and healthcare systems perspectives. Summary evidence tables for commonly used topical antimicrobials are included.

KEYWORDS: antimicrobial agents, iodine, polyhexamethylene biguanide, silver, topical agents, wound healing

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INTRODUCTION

As the population ages, chronic wounds represent an increased burden to patients, healthcare professionals, and healthcare systems. These chronic wounds (present for >6–12 weeks) take longer to heal than regular wounds and are often not treated effectively. Worldwide, annual estimates of chronic wounds include 4.5 million pressure injuries, 9.7 venous leg ulcers (VLUs; although there are many other leg ulcer etiologies), and 10 million diabetic foot ulcers. Diabetes incidence is growing worldwide, and healthcare systems are going to be challenged to effectively manage diabetic foot ulcers to prevent lower-limb amputations.

Critical colonization that can be treated topically and deep and surrounding infections are complications of chronic wounds that delay healing and increase associated healthcare costs.[1] Wound-related bacterial damage occurs in the surface compartment and can be treated topically; infections of the deep and surrounding compartments require systemic treatment.

To help illustrate the difference between infection in the superficial and deep tissue compartments, consider the analogy of a thin layer of soup in a bowl. The bottom of the bowl is a continuous compartment, with the sides representing the deep and surrounding compartments of a wound. The thin layer of soup represents the superficial critical colonization and changes on the wound surface that can be altered by topical therapy.

This article focuses on the superficial compartment and the appropriate use of topical antimicrobial therapies. The authors examined recent literature for the use of topical antimicrobials in chronic wounds. Topical antibiotic agents popular in the past such as mupirocin present several potential complications for patients with chronic wounds including bacterial resistance with a single mutation, contact allergy, inability to provide moisture balance or moisture reduction, and the lack of autolytic debridement. The last 40 years have seen the introduction of new classes of antiseptic dressings for critically colonized wounds.

Wound Classification for Healability

The wound bed preparation paradigm provides a comprehensive approach to chronic wound care that requires treatment of the wound cause and addressing patient-centered concerns (Figure 1).[2]

As part of the initial assessment, the ability of the wound to heal needs to be determined (Table 1). Classification of the wound as healable, maintenance, or nonhealable will impact the provider's specific choices for local wound care including topical antimicrobials and determining whether anti-inflammatory drugs may be beneficial.

Most patients can have the wound cause corrected and have adequate blood supply to heal (healable wound). However, not all wounds are healable because of systems or patient limitations. Patients may not be able to afford protective footwear or wear them at all times. Similarly, a patient with a VLU may not wear

Figure 1.
WOUND BED PREPARATION PARADIGM 2015

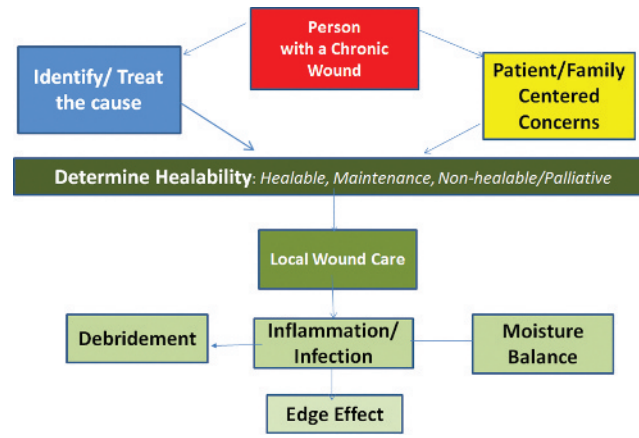

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Table 1.
WOUND HEALABILITY, DEBRIDEMENT, INFLAMMATION/INFECTION MANAGEMENT, AND MOISTURE BALANCE

Wound Healability Classification	Debridement	Inflammation/Infection Management	Moisture Management
Healable *Adequate blood supply; can correct the cause*	Active	Treat inflammation/infection (topically or systemic) including antisepsis as required	Moisture balance
Maintenance *Patient or healthcare system factors prevent healing*	Conservative (no disruption of surface blood vessels or bleeding)	Bacterial reduction—antisepsis	Moisture reduction
Nonhealable *Noncorrectable cause or lack of blood supply*	Comfort	Bacterial reduction—antisepsis	Moisture reduction

compression bandages or be unable to afford compression stockings to prevent recurrence.

With corrective interventions, a maintenance wound may be reclassified as healable, or maintenance therapy will aim to prevent wound deterioration. A patient with a major illness, inadequate or uncorrectable vascular ischemia, or multiple comorbidities (eg, cancer, uncontrolled autoimmune disease, or immunosuppressive drugs that may interfere with healing) can render a wound nonhealable.

NERDS

Five clinical signs, known as NERDS, can be used to identify critical bacterial colonization. A validation study confirmed that a wound possessing any 3 of the 5 NERDS criteria (73.3% sensitive, 80.5% specific) would be an indication to prescribe a topical antimicrobial agent (Figure 2).[3]

Each of the letters in the NERDS mnemonic represents a clinical sign:

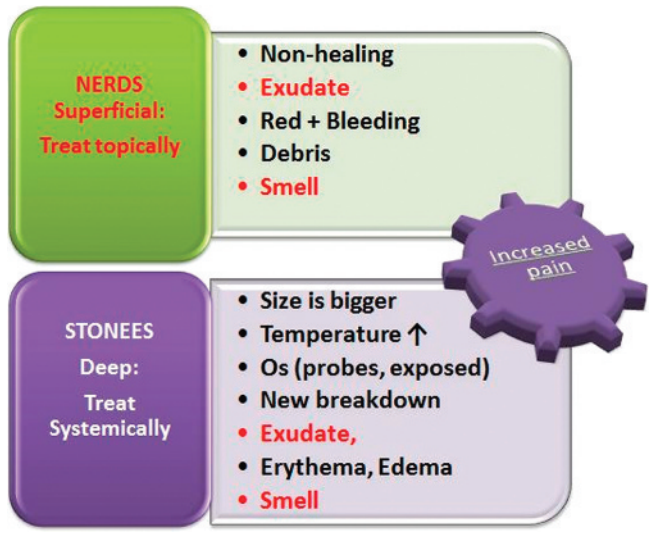
- **N**onhealing is a measure of the length × width that did not get smaller or increase in size over a 4-week period, indicating that the proinflammatory environment on the wound surface has prevented healing but that bacteria have not invaded the sides of the wound.
- **E**xudate is increased as a sign of irritation on the surface of the wound. The exudate may macerate the surrounding skin if the dressing cannot handle the increased discharge.
- **R**ed friable tissue on the wound surface indicates that vascular endothelial growth factor will produce more blood vessels than needed for mature granulation tissue. This is often bacterially stimulated and leads to a loose exuberant granulation tissue that may rise above the wound surface and will leave a blood stain when a dressing is removed. This tissue is different from firm pink granulation at a level surface with the wound edge that would promote re-epithelialization.
- **D**ebris on the wound surface (often yellow, brown, or black loose slough) is a result of surface cell death from local hostile conditions for viable cell growth and proliferation.
- **S**mell is the result of proliferation of gram-negative bacteria and anaerobes.

STONEES

By a similar analogy, a wound that presents with any 3 of the 7 STONEES criteria indicates the potential need for systemic therapy. Four of these criteria come from the marginal surface of the wound:

Size is increasing,

Figure 2.
THE CONCEPT OF NERDS AND STONEES SUPERFICIAL CRITICAL COLONIZATION VERSUS DEEP AND SURROUNDING INFECTION



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Temperature of the surrounding skin by infrared thermometry is greater than 3°F compared with the same area on the opposite side of the patient's body,[4]

Os is the Latin word for bone—probing or exposited—and increased **E**xudate or **S**mell as outlined above in the NERDS criteria.

New areas of breakdown with small satellite areas of breakdown in the wound margins, and

Erythema (often difficult to determine in brown or black skin) and/or

Edema of the surrounding skin (otherwise known as cellulitis).

Three criteria are derived from the deep wound compartment:

New or localized wound-related pain is an additional symptom that acts as supporting evidence to the clinical signs criteria for critical colonization or deep and surrounding infection.

RECENT LITERATURE ON TOPICAL ANTIMICROBIAL DRESSINGS

The authors searched MEDLINE (PubMed), the Cochrane Library, University of York Centre for Reviews and Dissemination database, and Google Scholar for systematic reviews, health technology assessments, high-quality randomized controlled trials (RCTs), and narrative review articles published from January 2012 to June 2017. Hand referencing was utilized. Burn, acute, traumatic, and postsurgical wound literature was excluded from this review. For topical antimicrobial therapies, where no high-quality studies could be found, lower-quality evidence was used to supplement findings along with expert knowledge. Search strings used are outlined in Table 2. This search was supplemented by landmark articles as per author judgment and a process similar to guideline synthesis.

TOPICAL ANTIMICROBIALS FOR HEALABLE WOUNDS

The following sections will discuss categories of topical antimicrobial therapies. Particular attention will be given to chemical composition, form, function, and clinical application. When there is not high-quality (RCT) evidence for an agent, this will be stated; however, the Cochrane reviews advise that "the lack of reliable evidence means that it is not possible to recommend discontinuation of any of the agents reviewed." Based on this, the authors have indicated the current logical best practices for each of the following commonly used topical antimicrobial agents: polyhexamethylene biguanide (PHMB), silver, iodine, methylene blue/crystal violet (MB/CV), and honey.

Polyhexamethylene Biguanide

In wound dressings, PHMB is a positively charged polymer with a hydrophobic backbone and cationic groups separated by hexamethylene chains.[5] This structure allows PHMB to bind to the negatively charged bacterial cell wall. When PHMB attaches to the acid membrane elements of the bacteria, the bacteria subsequently lose fluidity, causing separation of the individual membrane lipids and dissolution of the bacterial cell. This bactericidal mechanism means there are no residual organisms left alive to facilitate resistance.

Polyhexamethylene biguanide has been combined in gauze and foam dressing formats. Polyhexamethylene biguanide foam dressings are best utilized for healable surface wounds with exudate. Polyhexamethylene biguanide gauze packing is appropriate for a deep exudative wound that would benefit from antibacterial action. These dressings do not release the PHMB; rather, bacteria are killed in the compartment above the wound in the dressings. The effect is microbicidal for a broad spectrum of bacteria, yeast, and viruses.

One high-quality systematic review by Canadian authors[6] supports PHMB use in chronic wounds. A recent low-quality narrative review covers practical advice, suggesting that while PHMB is effective in preventing critical wound colonization it may not be effective in destroying the biofilm of colonized wounds.[7]

In a 4-week, 45-patient RCT, a nonrelease PHMB foam was compared with foam alone. Surrogate outcomes favored the use of PHMB foam.[5] The PHMB foam dressing was a significant predictor of reduced wound superficial bacterial burden (P = .016) at week 4 as compared with the foam alone. Pain reduction was also statistically significant at week 2 (P = .0006) and at week 4 (P = .02) in the intervention group. Polymicrobial organisms were recovered at week 4 in 5.3% of the PHMB foam dressing group patients versus 33% in the control group (P = .04). Subjects randomized to the PHMB foam dressing also had a 35% median reduction in wound size by week 4, compared with 28% in the control group, but this result did not reach statistical significance because of the small sample size of patients.

Additional supporting evidence is tabulated in Table 3.

Silver

Silver is ideally suited to healable wounds with critical colonization. It is an antibacterial agent in an ionized form that requires an aqueous environment. Ionized silver can attack at least 3 cellular components: cell membranes, cytoplasmic organelles, and DNA, so resistance is uncommon. Silver is most often combined with calcium alginates, hydrofibers, foams, and hydrogels and used as a coating on mesh-type structures with the appropriate moisture balance chosen for sustained release and exudate management to avoid periwound maceration. Topical silver can be combined with foam dressings so that the ionized silver can be released slowly in response to wound exudate. For nonhealable or maintenance wounds where moisture reduction is the

Table 2.
SEARCH STRINGS UTILIZED

Polyhexamethylene biguanide

Cochrane Library: polyhexamethylene biguanide

University of York Centre for Reviews and Dissemination: polyhexamethylene biguanide

PubMed: "Wounds and Injuries"[MeSH] AND "polyhexamethylene biguanide" + "wound" AND "polyhexamethylene biguanide"

Silver

University of York: ("silver") Limit 2014-2017, Canadian and International HTAs

Cochrane Library: ("silver") Limit = 2014–2017

Google Scholar: wound and silver and topical

PubMed: "Wounds and Injuries"[MeSH] and "silver" and "topical" Sort by: Relevance Filters: Publication date from 2014/01/01; humans; English

Also included articles from an earlier search strategy:

Cochrane Library: ("topical antibiotic" AND "wound") AND ("topical" AND "antimicrobial" AND "wound") AND ("topical" AND "antibiotic" AND "wound")

YORK CRT: ((antibiotic AND topical AND wound)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 2005 TO 2014

PubMed: (("Anti-Bacterial Agents"[MeSH]) AND "Wounds and Injuries"[MeSH]) AND "Administration, Topical"[MeSH]))

Google Scholar: ("topical antibiotic" AND "wound care") AND ("topical antibiotic" AND "wound care" AND "acute")

Honey

University of York: topical OR superficial OR epidermal OR critical AND colonization OR biofilm AND honey

PubMed: "Wounds and Injuries"[MeSH] AND honey (2014-; English, human)

topical OR superficial OR epidermal OR critical AND colonization OR biofilm AND honey (2014-; English, human)

Google Scholar: topical OR superficial OR epidermal OR critical AND colonization OR biofilm AND honey (2014-) sorted by relevance (went up to page 7 (including page 7))

Chlorhexidine

University of York: ("chlorhexidine") Limit 2014-2017

Cochrane Library: ("chlorhexidine") Limit = 2014-2017

Google Scholar: "wound and chlorhexidine" Limit = 2014-2017, exclude patents and citations

PubMed: "Chlorhexidine"[MeSH] AND "Wounds and Injuries"[MeSH] AND (("2014/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Methylene Blue/Crystal Violet

University of York: ("methylene blue") Limit 2014-2017

("gentian violet") Limit 2014-2017

Cochrane Library: ("methylene blue") Limit = 2014-2017

("gentian violet") Limit = 2014-2017

Google Scholar: "wound and methylene blue" Limit = 2014-2017, exclude patents and citations

"wound and gentian violet" Limit = 2014-2017, exclude patents and citations

PubMed: "Wounds and Injuries"[MeSH] AND "Methylene Blue"[MeSH] AND (("2014/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

"Wounds and Injuries"[MeSH] AND "Gentian Violet"[MeSH] AND (("2014/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Iodine

University of York: topical OR superficial OR epidermal OR "critical colonization" OR biofilm AND iodine

Pubmed: "Wounds and Injuries"[MeSH] AND iodine (2014-; English, human)

topical OR superficial OR epidermal OR "critical colonization" OR biofilm AND iodine (2014-; English, human)

Google Scholar: topical OR superficial OR epidermal OR "critical colonization" OR biofilm AND iodine (2014-) sorted by relevance (went up to page 7 (including page 7))

Table 3.
RECENT EVIDENCE ON POLYHEXAMETHYLENE BIGUANIDE TOPICAL DRESSINGS

PHMB foam may be used for healable wounds with exudate; PHMB gauze and packing may be used for healable, nonhealable, and maintenance wounds with exudate. PHMB foam dressings may reduce wound size, decrease bacterial count, and decrease pain in wounds with superficial bacterial burden.

Study	Findings	Conclusions
To et al[6] A 2016 systematic review of English-language RCTs covering publications between 1946 and February 2014 on the effectiveness of topical PHMB for the treatment of chronic wounds	• 6 of 1,725 articles met inclusion criteria • 3 single-center trials and 3 multicenter trials • Sample sizes ranged from 10 to 40 adult chronic wound participants • 2 studies: "PHMB dressings achieved a faster, more substantial reduction in bacteria count"[6] • 2 studies had a reduction in the number of polymicrobial organisms • 2 studies: PHMB dressings eradicated MRSA from pressure ulcer tracheostomy sites • 4 studies demonstrated pain reduction from the use of PHMB agents	"The existing evidence shows that topical PHMB may promote healing of chronic stalled wounds, reduce bacterial burden, eliminate methicillin-resistant *Staphylococcus aureus*, and alleviate wound-related pain."[6]
Hurlow[7] A narrative 2017 review on the benefits of PHMB in wound care	• Reviewed in vitro and in vivo studies • Cites MRSA growth suppression effect of PHMB by Kirker et al[8] • Cautions toxicity may be an issue in some patients if PHMB is used alone	"PHMB-impregnated dressings appear to be very effective as a barrier to wound colonization and infection."[7]

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; PHMB, polyhexamethylene biguanide; RCTs, randomized controlled trials.

target, silver is not indicated because silver cannot remain in an ionized state on a dry surface.[2]

Topical silver dressing studies were extensively reviewed by Leaper[9] in an international consensus published in 2012, which concluded that silver dressings may be effective at reducing bacterial burden in critically colonized wounds.

Münter et al[10] reported surrogate wound outcomes in a 4-week trial of 619 patients comparing silver foam versus local best practices. The silver foam had a significantly higher median reduction in ulcer area compared with the control group (47.1% vs 31.8%; $P = .0019$). The silver group also had significantly improved ($P < .05$) exudate handling, ease of use, odor reduction, and pain control.

Carter et al[11] in 2010 conducted a systematic review of 10 leg ulcer RCTs with 38 to 619 patients in each of the studies. This review found some evidence that silver-impregnated dressings improved the short-term healing of leg ulcers, especially in the first 4 weeks; however, the longer-term effectiveness requires more study.

The more recent publications on silver as a topical antimicrobial agent, summarized in Table 4, emphasize the gaps in current knowledge and the need for further studies. There are also recommendations for decision makers that cost-effectiveness and patient preference should be key elements for dressing selection.

Iodine

Iodine is a natural, nonmetallic element that is essential for the production of thyroid hormone. Iodine has several antimicrobial actions including blocking bacterial cell efflux pumps, interfering with cellular respiratory processes, changing DNA structure, and denaturing cellular proteins and enzymes. Patients on iodine for large wounds or extended periods should have thyroid function tests at regular intervals as hypothyroidism or hyperthyroidism can be induced by iodine wound dressings.[2]

Iodophors, developed in the 1950s, are safer, slow-release iodine delivery systems.[18] The 2 most commonly used iodophors in modern wound dressings are povidone iodine (PVP-I) and cadexomer iodine. Povidone iodine is a chemical complex of polyvinylpyrrolidone and elemental iodine. It is available as a slow-release dressing (knitted viscose mesh) in some regions (eg, Canada and Europe), along with 7.5% to 10% solution formats, creams, ointments, and sprays. Cadexomer iodine is an absorptive polysaccharide that absorbs exudate and provides

Table 4.
RECENT EVIDENCE ON SILVER-BASED DRESSINGS

This table covers silver dressings indicated for healable wounds with critical colonization. Cochrane Reviews, systematic reviews, and RCTs were reviewed to evaluate current evidence regarding the use of silver as a topical treatment for wounds. Highly-quality Cochrane Reviews found uncertain evidence for the use of silver-based dressings for a variety of wounds including surgical, pressure, and venous ulcers and fungating wounds.

Study	Findings	Conclusions
O'Meara et al[12] This updated Cochrane Review conducted in 2014 included 45 RCTs of 4,486 participants on antibiotics and antiseptics for VLUs.	• Examined silver- and antibiotic-containing ointments (12 RCTs) • Silver-based products: no difference in healing with silver sulfadiazine or when different brands of silver-impregnated dressings compared with nonantimicrobial dressings or honey in promoting healing of VLUs	"Lack of reliable evidence means that is it not possible to recommend the discontinuation of any of the agents reviewed."[12] "Current evidence does not support the routine use of honey- or silver-based products."[12]
Leaper[13] This 2011 editorial provides expert opinion and gives context to recent evidence, especially some of the difficulties with current research and reliance on only RCT meta-analysis/ Cochrane Reviews.	• Use of topical antimicrobials, specifically antiseptics (eg, silver) rather than antibiotics, should be supported because of (1) reduction in the risk of critical colonization (2) refuting antimicrobial resistance (3) reduction in the risk of biofilm formation (4) aiding debridement (5) preparing the wound bed (6) infection prevention	"[The] rise of antibiotic-resistant organisms, especially methicillin-resistant *Staphylococcus* infection (MRSI), is a major reason to revisit use of topical antimicrobials."[13]
Adderley and Holt[14] This is the third updated Cochrane Review (2014) on topical agents and dressing on fungating wounds.	• 4 RCTs (164 people) with 2 involving silver dressings • More patients had decreased malodor in the foam dressing and silver group than in the foam dressing without silver group (P = .049). • No statistically significant difference with regard to exudate, malodor, and wound pain for manuka honey–coated dressings than with nanocrystalline silver-coated dressings. • Weak evidence to suggest that foam dressings containing silver may be effective in reducing malodor	"Insufficient evidence in this review to give a clear direction for practice with regard to improving quality of life or wound symptoms in associated with fungating wounds."[14]
Dumville et al[15] A Cochrane Review in 2014 (29 RCTs) on dressings for the prevention of SSI, including silver-containing dressings following clean and potentially contaminated surgery	• A relative risk of 1.11 of SSI for silver-containing dressings vs basic wound contact dressing for clean surgery. **Grade:** very low-certainty evidence • A relative risk of 0.83 of SSI for silver-containing dressings vs basic wound contact dressing for potentially contaminated surgery. **Grade:** very low-certainty evidence	"It is uncertain whether covering surgical wounds healing by primary intention with wound dressings reduces the risk of SSI, or whether any particular wound dressing is more effective than others in reducing the risk of SSI, improving scarring, reducing pain, improving acceptability to patients, or is easier to remove. Most studies in this review were small and at a high or unclear risk of bias…. Based on the current evidence, decision makers may wish to base decisions about how to dress a wound following surgery on dressing costs as well as patient preference."[15]

(continues)

Table 4.
RECENT EVIDENCE ON SILVER-BASED DRESSINGS, CONTINUED

This table covers silver dressings indicated for healable wounds with critical colonization. Cochrane Reviews, systematic reviews, and RCTs were reviewed to evaluate current evidence regarding the use of silver as a topical treatment for wounds. Highly-quality Cochrane Reviews found uncertain evidence for the use of silver-based dressings for a variety of wounds including surgical, pressure, and venous ulcers and fungating wounds.

Study	Findings	Conclusions
Norman et al[16] A Cochrane Review in 2016 (12 RCTs of 576 participants) on antibiotics and antiseptics for Stage ≥2 pressure ulcers	• Povidone iodine vs silver sulfadiazine: 63.6% of ulcers treated with povidone iodine were judged to be free of infection compared with 100% ulcers treated with silver sulfadiazine. **Grade:** low-quality evidence • Silver mesh vs silver sulfadiazine: no complications as a result of treatment in either group; 34.6% reduction in mean ulcer area in the silver mesh group compared with 20.1% in the silver sulfadiazine group. Mean costs were $263 for silver mesh vs $1,812 for silver sulfadiazine. • Silver alginate vs silver sulfadiazine: 44.27% reduction in mean ulcer area in the silver alginate group compared with 51.07% in the silver sulfadiazine group. Mean costs were $377 for silver alginate vs $467 for silver sulfadiazine. • Silver sulfadiazine vs saline: 78.6% of ulcers treated with saline were free of infection compared with 100% ulcers treated with silver sulfadiazine. **Grade:** low-quality evidence	"The relative effects of systemic and topical antimicrobial treatments on pressure ulcers are not clear. Where differences in wound healing were found, these sometimes favored the comparator treatment without antimicrobial properties."[16]
Tricco et al[17] A systematic review in 2015 that examined effective interventions to treat complex wounds, including silver dressings for unspecified mixed complex wounds	• One meta-analysis supported that "topical silver and silver dressings were found more effective than placebo or conservative wound care or nonsilver therapies," and "Silver-impregnated dressings were more effective than dressings not containing silver in a meta-analysis." • For mixed complex wounds, silver dressings were found to be more effective than no treatment.	"Our results confirm that there are numerous interventions that can be utilized for patients with complex wounds. However, few treatments were consistently effective throughout the literature."[17]

Abbreviations: RCTs, randomized controlled trials; SSI, surgical site infection; VLUs, venous leg ulcers.

autolytic debridement along with a slow release of iodine into the wound bed.[18]

In a recent review of iodine, the following concluding statement summarized the literature review[19]:

"Although it has been speculated that iodine delays healing and is cytotoxic, there is substantial evidence to suggest that the commonly used low-concentration, slow-release iodophors improve healing rates and are effective as highly potent antimicrobials with a broad spectrum of activity, including antibiotic-resistant strains such as MRSA [methicillin-resistant *Staphylococcus aureus*]. It is unfortunate that the concerns about iodine are based on studies that are so varied in method and design that it is difficult to draw reliable comparisons and conclusions…. but it is now widely accepted that slow-releasing iodophor antimicrobials are safe and have minimal detrimental impact on wound healing."

The recent evidence summarized in Table 5 adds further support for cadexomer iodine for the improved healing of VLUs and the utility of PVP-I for nonhealable or maintenance wounds.

Table 5.
RECENT EVIDENCE ON IODINE

Iodine (especially cadexomer iodine) can be used for healable wounds; nonhealable and maintenance wounds may benefit from PVP-I, especially in delayed-release format. There is high-quality evidence in the form of a Cochrane Review and a *JAMA* clinical evidence synopsis on the utility of using cadexomer iodine in the treatment of venous leg ulcers.[12,20] In addition, there is evidence in the form of a retrospective chart audit that PVP-I may be efficacious in the treatment of diverse maintenance and nonhealable ulcers.[21]

Study	Findings	Conclusions
O'Meara et al[12] A Cochrane Review in 2014 that summarized the research on various antibiotics and antiseptics in promoting the healing of VLUs	• Analysis of 11 RCTs on cadexomer iodine vs standard care found that more VLUs healed with cadexomer iodine vs standard care by 4-12 wk. • Analysis of 6 RCTs on PVP-I found that there was no difference in complete healing when PVP-I was compared with hydrocolloid, moist wound healing dressings, or foam dressings according to wound status.	This Cochrane Review suggests that some evidence supports the use of cadexomer iodine (but not PVP-I) to improve healing of VLUs over standard care.
O'Meara et al[20] A clinical evidence synopsis published by O'Meara, Richardson, and Lipsky in *JAMA* in 2014 on treatments of VLUs	• 4 pooled RCTs (212 patients) suggest that cadexomer iodine was associated with better healing rates but more adverse events (such as pain and itching) than standard care: "Single RCTs demonstrated no association with better healing for cadexomer iodine compared with silver dressings; PVP-I compared with usual care, or mupirocin compared with placebo."[20]	This *JAMA* clinical evidence synopsis suggests that treatment with cadexomer iodine may be associated with improved healing rates for VLUs but more adverse events as compared with standard care.
Woo[21] A retrospective chart audit in 2014 on the efficaciousness of PVP-I in the management of maintenance or nonhealable wounds	• Charts from 30 patients from a Canadian Wound Clinic with a total of 42 wounds were reviewed • All wounds were treated with topical PVP-I for 6 mo with monthly monitoring. • 28.6% of wounds (n = 12) completely closed and 45.2 % (n = 19) of wounds decreased in size at the 6-mo mark • Some transient burning of stinging and documented cases of irritant and potential allergic dermatitis	Use of PVP-I for maintenance of nonhealable ulcers decreased wound size in 73% of wounds over a 6-mo period.
Norman et al[22] This Cochrane Review in 2016 summarized 11 RCTs of 886 participants comparing various antibiotics and antiseptics for promoting healing of surgical wounds by secondary intention	• In 2 studies, iodine preparation vs no antiseptic treatment to promote healing by secondary intention • No clear evidence could be found to support one treatment over the other	"There is no robust evidence on the relative effectiveness of any antiseptic/antibiotic/antibacterial preparation evaluated to date for use on surgical wounds healing by secondary intention."[22]

Abbreviations: PVP-I, povidone iodine; RCTs, randomized controlled trials; VLUs, venous leg ulcers.

Methylene Blue and Crystal Violet Foam Dressings

This product is a relatively nonrelease foam dressing with 2 agents, MB and CV, which produce a redox (oxidation-reduction) environment inhibiting the growth and survival of bacteria. There are 2 foam formats. The original polyvinyl alcohol foam needs to be partially hydrated to bind surface slough and provide autolytic debridement. The foam structure facilitates wicking and moisture retention/moisture balance. The more traditional polyurethane dressing is similar to most other foam products in its fluid-handling characteristics without autolytic debridement.[2]

Recent evidence on MB/CV is outlined in Table 6.

Honey

Honey has been used in wound care for centuries because of its antibacterial and anti-inflammatory properties. Its acidic pH (3.2–4.5) and high sugar content (osmolality) make the local wound environment hostile to bacteria. Hydrogen peroxide released by honey is antibacterial; however, this action can be neutralized by blood, serum, and wound exudate. Manuka trees and some other *Leptospermum* genus plants have bee-derived honey that also contains methylglyoxal, an additional and more stable antimicrobial component. Honey may lose its antibacterial action when diluted with wound exudate, but this may not increase the incidence of bacterial resistance.[2]

Medical-grade honey should be used instead of honey from food sources. This is because bacterial spores, including *Clostridium* species, can persist in honey and have the potential to cause disease if activated.

Recent literature is summarized in Table 7. The following quote best summarizes the evidence on the use of honey in chronic wounds: "Current evidence does not support the routine use of honey. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed."[12]

There may still be a role for honey in specialized patients where autolytic debridement is required for hard, fibrous surfaces or in wounds that need an increased moisture content.[25]

WOUND-PACKING MATERIALS

Wound-packing materials are required for deeper wounds (eg, Stages 3 and 4 pressure injuries). When packing a wound, clinicians need to match form to function. The packing materials listed in Table 8 are related to their key properties. Dry gauze will absorb exudate, but it is not antibacterial, and bacteria can grow

Table 6.

RECENT EVIDENCE ON METHYLENE BLUE AND CRYSTAL VIOLET

These dressings are suitable for antibacterial action above the wound surface. They are indicated for exudating wounds with critical colonization and achieving moisture balance. The PVA foam provides autolytic debridement. Two case series[23,24] found that the use of methylene blue and gentian violet dressings may be suitable for managing diverse chronic wounds. Both case series found that patients had fewer signs and symptoms of wound infection and decreased wound size.

Study	Findings	Conclusions
Coutts et al[23] A nonrandomized case series of 15 patients (8 DFUs and 7 leg ulcers) evaluating antibacterial dressing made of PVA foam bound with gentian violet and methylene blue as well as compression for venous leg ulcers and offloading devices for DFUs	• 47% of patients had a decrease in NERDS signs at the end of the study period • Improvements in the pain score were noted in some patients (38% reported a decrease in pain), and decrease in wound size was also noted in 57% of patients	• An antibacterial foam dressing consisting of PVA foam bound with gentian violet and methylene blue "showed encouraging results and may be a suitable option for lower-extremity chronic wounds demonstrating an increased superficial bacterial burden."[23] • The antibacterial foam also appears to provide autolytic debridement.
Woo and Heil[24] A prospective, nonrandomized case series based on 29 Canadian patients with chronic wounds exhibiting signs of local infection. Wounds were managed with antibacterial foam dressing containing methylene blue and gentian violet.	• At week 4, wound surface area was reduced by an average of 42.5% (21.4–12.3 cm^2), and wounds went from an average of 3.6 wound infection signs and symptoms to 0.9.	Foam dressings containing methylene blue and gentian violet may be efficacious in improving healing and reducing signs and symptoms of wound infection.

Abbreviations: DFUs, diabetic foot ulcers; PVA, polyvinyl alcohol; RCTs, randomized controlled trials.

Table 7.
RECENT EVIDENCE ON HONEY

Honey is indicated for hard, firm eschars, and selected cases of critically colonized wounds. There is currently little evidence to support the use of honey dressings for chronic wounds. A recent Cochrane Review found no benefit in using honey dressings for VLUs.[12] Furthermore, while a case-control study[26] found no difference in healing of bedsores with the use of honey dressings versus povidone iodine, this is not sufficient evidence to recommend the routine use of honey dressings.

Study	Findings	Conclusions
Khadanga et al[26] A low-quality descriptive, case-control study published in 2015 at 1 tertiary heath center in India conducted over 1 y (N = 40 persons aged ≥15 y) on the use of honey vs povidone iodine in patients with bedsores	• Patients in the honey group reported significantly less pain by day 10 (as measured by the visual analog scale). The decrease in the size of the wounds between the 2 groups was not statistically significant, and the bacterial load by day 10 was similar in both groups.	Decrease in wound size and bacterial burden at day 10 was similar between povidone iodine and honey.
O'Meara et al[12] An updated Cochrane Review in 2014 that included 45 RCTs of 4486 participants on antibiotics and antiseptics for VLUs.	• 2 RCTs were reported on honey products and found no difference in time to healing or complete healing between wounds treated with honey products vs usual care.	"Current evidence does not support the routine use of honey. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed."[12]

Abbreviations: RCTs, randomized controlled trials; VLUs, venous leg ulcers.

in the gauze and contaminate the wound surface. Moist saline gauze will donate moisture to the wound surface, but again, it is not antibacterial and may facilitate wound contamination. With low host resistance, contamination can lead to critical colonization, then potential deep and surrounding infection.

Both PHMB gauze and iodine-saturated ribbon gauze are antibacterial. The PHMB gauze will sterilize the compartment above the wound by killing bacteria that penetrate the gauze. This mechanism relies on host resistance to clear the bacteria on the wound surface with a decreased number of contaminating organisms. Iodine-saturated ribbon gauze will deliver iodine to the surface of the wound, as long as there is an orange color in the gauze. There is probably less toxicity from PVP-I on the wound surface than predicted by in vitro studies.[19] As soon as critical colonization is reversed, PHMB ribbon gauze may prevent surface bacterial contamination and relies on host resistance to prevent the return of critical colonization.

TOPICAL ANTISEPTIC AGENTS

Topical antiseptic agents are often used in maintenance and nonhealable wounds where tissue toxicity may not be as important as the agents' antibacterial properties.

Chlorhexidine is related to PHMB and is available in antiseptic preparation solutions for the operating room or minor surgeries; mouthwash formulations with aqueous bases that will not burn or sting open skin; and petrolatum-type tulle dressings that have a nonrelease format to minimize bacteria in the compartment above the wound.

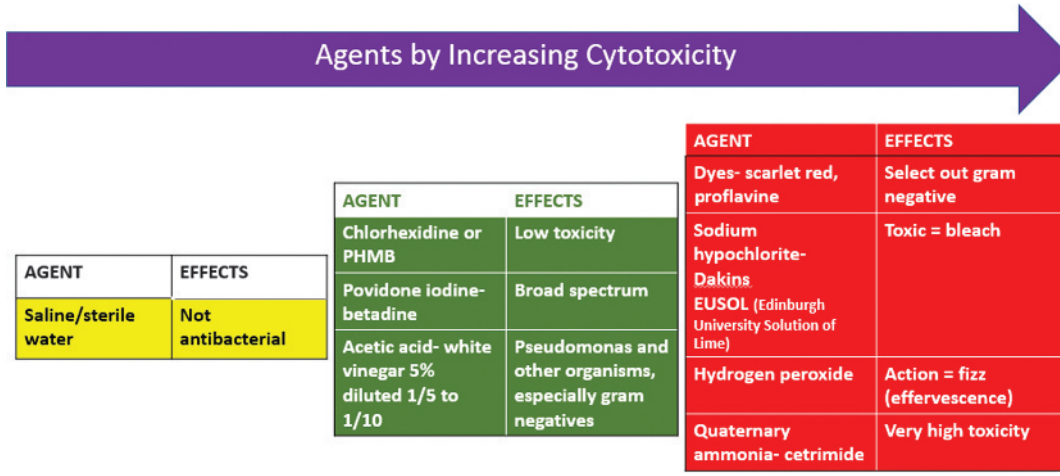
Polyhexamethylene biguanide is often used as a preservative in eye and ear preparations, which adds indirect evidence to its

Table 8.
THE PROPERTIES OF COMMON WOUND-PACKING MATERIALS

Wound-Packing Material	Properties
Dry gauze	Absorbs exudate
	Not antibacterial
Moist saline gauze	Donates moisture and hydrates wound
	Not antibacterial
PHMB gauze	Absorbs exudate
	Provides antibacterial activity above the wound
	Nonrelease, no tissue toxicity
Povidone iodine–soaked gauze	Iodine delivered to the wound surface
	Penetrates biofilm and decreases surface bacteria
	Some potential tissue toxicity

Abbreviation: PHMB, polyhexamethylene biguanide.

Figure 3.
SELECT ANTISEPTIC AGENTS LISTED BY INCREASING CYTOTOXICITY



NB: Agents are color-coded by safety profile and antiseptic action. Green = low toxicity potential; yellow = no antibacterial effect; red = high toxicity potential.

low toxicity. It is a large molecule, so percutaneous penetration is minimal.

Povidone iodine may also be used to paint around the edge of a maintenance wound or an area of gangrene. The infection of the deep and surrounding tissue will usually begin at the proximal edge of the gangrene, and this is where it is more important to paint the PVP-I to minimize bacterial invasion.

Compresses with diluted acetic acid (0.5%–1%) can lower wound pH and create a hostile environment for *Pseudomonas* and other bacteria that prefer an alkaline environment. *Pseudomonas* can often be treated topically, preferably with 2 agents (eg, acetic acid compresses and PVP-I or cadexomer iodine). If gram-positive and other bacteria are treated systemically, it is often not necessary to use oral agents against *Pseudomonas*, even for diabetic neurotrophic foot infections.[27] More recently, hypochlorous acid has been utilized in some clinics in a similar fashion.

Other antiseptic agents in the red categories of Figure 3 have higher tissue toxicity and are not currently recommended for routine use in chronic wounds.

CONCLUSIONS

Topical antiseptic agents are recommended for critically colonized chronic wounds. Patients should be carefully monitored every 2 to 4 weeks, and if the critical colonization persists, deep and surrounding infection, inadequate treatment of the cause, or patient-centered concerns should be reassessed. For all wounds, cleansing with agents that lower surface pH (into the acidic range) may aid in bacterial reduction, especially for gram-negative bacteria including *Pseudomonas*.

For healable wounds, moisture balance can be complemented with local care for critical colonization. Clinical options include silver dressings, slow-release iodine, medical-grade manuka honey, nonrelease PHMB, or MB/CV dressings. Additional criteria for dressing selection may be based on formulary availability, cost-effectiveness, and patient preference.

Nonhealable or maintenance wounds are best served with moisture reduction and topical antiseptics that may include PVP-I or chlorhexidine (or its derivative PHMB). Each patient must be considered individually, and wounds assessed for pain, local wound fragility, and tissue viability in order to make the best choice for local wound care utilizing the wound bed preparation paradigm.

PRACTICE PEARLS

- Topical antimicrobial use should be based on 3 or more NERDS signs.
- Silver is anti-inflammatory but needs an aqueous base, not a dry environment.
- Iodine is effective in aqueous and dry environments and penetrates biofilms because of its proinflammatory properties.
- Polyhexamethylene biguanide is a nonrelease antimicrobial agent that provides bacterial action above, but not on the surface of, wounds.
- Honey is antibacterial and provides oncolytic debridement, but more evidence is required to support routine chronic wound usage.

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