New Twist on an Old Favorite: Gentian Violet and Methylene Blue Antibacterial Foams

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Significance: Absorptive antibacterial dressings that assist in controlling bioburden without risks of cytotoxicity or residual absorption can be effectively used for prolonged periods throughout the wound healing continuum.

Recent Advances: Until recently, gentian violet and methylene blue (GV/MB) antibacterial dressings have been commercially available only in polyvinyl alcohol (PVA) foam; polyurethane (PU) foam bonded with GV and MB with thin film backing is now commercially available. GV/MB PU foam does not require hydration or a necessary secondary dressing. GV/MB PVA and PU foam dressings were recently granted FDA clearance as antibacterial dressings, as opposed to bacteriostatic dressings as previously classified. Within the class of antibacterial dressings, GV/MB foam dressings are of lower cost alternative to silver- or iodine-based antibacterial dressings with no risk of absorption of any of the foam components into the tissues.

Critical Issues: Control of wound bioburden levels by antibacterial agents and absorption of excess exudate are crucial in preventing infections that drastically increase the price of wound care. Use of GV/MB dressings may improve wound healing outcomes and decrease overall costs through super absorption, promotion of autolytic debridement, bioburden reduction, ease of use, and decreased dressing change frequency.

Future Directions: Evolution in resistant bacterial strains will drive continual changes in advanced wound care products. Demand will increase for economically priced, versatile wound care dressings that assist in debridement, maintain a moist wound environment, absorb and trap bacterial debris, and decrease dressing change frequency.

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SCOPE AND SIGNIFICANCE

With the ever increasing number of antibiotic resistant microbes, the need for topical treatments that limit bacterial colonization in wounds is paramount. Antibacterial dressings play an increasingly important role in bioburden control and wound healing. A foam dressing bound with gentian violet and methylene blue (GV/MB) antibacterial agents (Hydrofera Blue; Hollister Wound Care, Libertyville, IL) has been shown to be effective against a wide spectrum of microorganisms found in wounds, including methicillin-resistant *staphylococcus aureus* (MRSA), vancomycin-resistant *enterococcus* VRE and Candida. We review the mechanisms and history of two different GV/MB foams and our experience with these foams in treating chronic and acute wounds in a large university teaching hospital.

TRANSLATIONAL RELEVANCE

The majority of scientific studies on antibacterial agents, including the combination of MB and GV, have been conducted *in vitro*. The FDA has

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cleared GV/MB dressings as an antibacterial based on *in vitro* evidence. These *in vitro* studies do not account for the possible dilution effects of various types of wound exudates and fluid content that may be present in a clinical scenario. Higher concentrations of antibacterial agents may be required *in vivo* to achieve similar antibacterial activity to that observed *in vitro*.[1] To complete the chain of evidence supporting translational relevance, controlled prospective clinical research is warranted to confirm the antibacterial nature of GV/MB dressings on various human wound types.

CLINICAL RELEVANCE

The rising cost of health care is prompting patient care personnel to take a closer look at cost-effective wound care products that can be used across the spectrum of wound healing—from debridement to closure. Effective use of topical antimicrobials to prevent or treat colonized or critically colonized wounds is crucial to decrease the overuse of antibiotics being used to treat wounds that are not yet clinically infected. Accomplishing this would allow antibiotics to be better utilized for "clinically critical situations."[2] GV/MB foam dressings are indicated for colonized and critically colonized wounds with varying levels of exudate.

BACKGROUND

All wounds contain bacteria. In most cases, the wound bioburden and host's immune system are in balance, and the wound heals successfully. However, in cases where the balance shifts in favor of the bacteria, or if wound healing is compromised, bacteria multiply and attack tissues, resulting in a prolonged inflammatory response, tissue damage, delayed healing, and potential systemic illness. If it is determined that the wound is not healing because of a rising bacterial load, immediate intervention with an antibacterial dressing is recommended.[3] Importantly, however, antibacterial dressings should only be used after careful assessment of the whole patient and wound, and after effectively addressing all causes of delayed healing, to achieve preestablished goals of treatment, closure, and cost-effectiveness in clinical practice.[4,5]

For purposes of this article, antibacterial dressing refers to wound dressings with an incorporated antibacterial agent, as opposed to an antibiotic. Whereas in the past, silver, iodine, and topical antibiotic dressings were the treatment of choice for infected/colonized wounds, recent advances in antibacterial technology have led to the development of numerous dressings incorporating antibacterial agents, such as silver, cadexomer iodine, polyhexamethylene biguanide, and honey.[6] While the incorporated antibacterial agent typically displays broad spectrum nonselective antimicrobial activity, prolonged use of any of these agents has generally been limited due to several drawbacks, including potential cytotoxicity.[7,8]

The FDA first cleared the GV/MB polyvinyl alcohol (PVA) foam dressing as a bacteriostatic dressing in 2003 for use on pressure ulcers, diabetic ulcers, venous stasis ulcers, arterial ulcers, superficial burns, donor sites, postsurgical incisions, trauma wounds, abrasions, and lacerations. Bacteriostatic refers to dressings capable of inhibiting the growth or reproduction of bacteria. GV/MB-impregnated polyurethane (PU) foam dressing (Hydrofera Blue Ready; Hollister Wound Care) with a moisture retentive backing was developed in 2013. The GV/MB PU dressing does not need to be hydrated, whereas the GV/MB PVA foam requires saline hydration. In 2014, the FDA re-classified both GV/MB PVA and PU foams as antibacterial dressings, indicating that they are capable of destroying bacteria and suppressing the growth of bacteria and their ability to reproduce.

Beneficial effects of MB and GV on microbial reduction have been documented as early as 1902.[9,10] These organic antimicrobial dyes have been used for many years in the clinical setting with minimal toxicity to humans.[9,11,12] The combination of MB, GV, and PVA foam was originally used as a double-dye method of inactivating pathogens to purify blood.[13] Blood was seeded with these dyes and passed through white PVA foam as a filter. The pigments and the pathogens became trapped in the foam, and the blood was purified. In addition, the red blood cells were left unharmed and a high percentage of essential proteins were recovered—both of which suggest selectivity. The resulting blue foam was found to be able to inactivate pathogens on its own,[13] thus leading to the development of the current antibacterial foam.

In a recently reported case series, authors found currently marketed PVA and PU GV/MB antibacterial foam dressings to be safe and viable in managing chronic lower extremity and diabetic foot ulcers.[11] GV/MB foam is one of very few antibacterial dressings that can be used in conjunction with enzymatic debriding agents, growth factors, or hydrogels without inhibiting their actions.[4,14] Evidence that GV/MB dressings may support autolytic debridement has been presented in the literature[11] and is shown in Fig. 1A–B—suggesting potential dressing viability from "start to finish" in

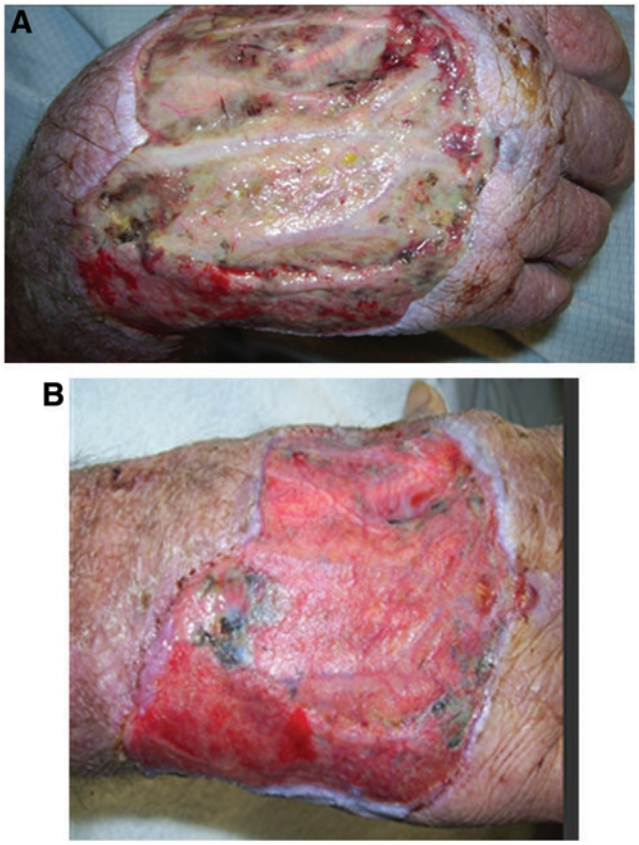

Figure 1. Large hand hematoma in patient with ARDS. **(A)** A 76-year-old male with ARDS presented with a large hematoma on top of hand caused by repeated trauma with bed rail. Patient was on multiple medications, including corticosteroids and blood thinners. The hematoma was debrided and a silver gel was used for moist wound healing. After 5 days, additional problems developed, including slough over the wound surface and macerated edges. GV/MB dressing was applied to decrease bacterial load, absorb excess drainage, and assist in autolytic debridement. **(B)** Nine days following GV/MB dressing application, the wound bed was clean and granulating. Reprinted with permission from Hollister Wound Care. ARDS, acute respiratory distress syndrome. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

wound healing and decreased need for adjunctive enzymatic debriding ointment.

DISCUSSION

Limitations of systemic and topical antibiotics

Systemic antibiotics are indicated for overt wound infection and to decrease the possibility of systemic infection, but they are largely ineffective in wounds in which species of bacteria have not been identified.[15] In addition, chronic wound care patients often have compromised circulation and edema, decreasing the amount of oxygen delivery to tissues and encouraging growth of bacteria, especially anaerobes, which are common in many infected wounds.[16] Systemic antibiotics are not as effective as in conditions of limited circulation.

Antibiotic ointments are frequently prescribed for topical treatment on purported infected wounds, despite known limitations. The problem with use of antibiotic ointments on noncultured wounds is that they are highly selective, and each antibiotic is effective only against certain bacteria that are sensitive to that particular antibiotic. Overuse of topical antibiotics can lead to allergic contact dermatitis (ACD), which could lead to a cross allergy to another antibiotic.[17] Although double and triple antibiotic ointments, still commonly prescribed for wound care, have shown 24-h duration, broad-spectrum bactericidal and bacteriostatic efficacy against organisms *in vivo*,[18] ointment ingredients, bacitracin and neomycin, have been implicated as sensitizers in ACD.[19,20] ACD can complicate and delay wound healing and therefore increases the overall cost of care.

A growing body of evidence that suggests increasing rates of sensitivity to topical antibiotics reported in the literature may be related to wound duration, therefore over exposure to certain antibiotic ointments.[21] In addition, antibiotic dressing changes are usually required once or twice daily, which can cause increased irritation of wound site and discomfort for the patient. With moderate to large amounts of exudate, the ointment may not be effective as its potency decreases when mixed with the exudate. All these negative side effects should discourage prolonged use of topical antibiotic ointments. Best results are achieved following a wound culture and sensitivity test and administration of appropriate topical culture-specific antibiotics[22,23]; however, this process requires time and expense.[19]

Use of antibacterial dressings, such as GV/MB foam, appears to be increasing based on the ability of these technologies to promote broad-spectrum action, control bioburden, and reduce incidence of resistance. In the opinion of the author, wound care clinicians should be seeking and providing support and education to transition from traditional wound care regimens toward modern wound dressings for improved healing, decreased pain, better quality of life for the patient, and decreased cost of care for chronic wounds.

PU and PVA foam material differences

Classic GV/MB PVA foam dressings are constructed of cross-linked PVA with three-dimensional open-cell structure similar to natural sea sponges. This dressing needs to be hydrated before application. GV/MB PVA foam is uniquely manufactured using proprietary technology, and it differs from other PVA foams; the micropore structure is designed specifically for the purpose of continu-

ous absorption and wound care. Inherent benefits of this polymer include large absorption capacity and strong tensile strength.[24]

Like the PVA, GV/MB PU foam dressings are hydrophilic. The PU foam is open-cell reticulated foam with pore size and structure specifically designed for wound care. However, PU differs in that it is flexible with no hydration required before application. GV/MB PU foam dressings also have a thin foam backing, which alleviates the need for a secondary dressing. GV/MB PU foam is not as strong or absorbent as PVA foam, but its absorbency is comparable to other antimicrobial foam dressings (Fig. 2).

Mechanisms of action of GV/MB antibacterial foams

Although the mechanisms of action behind the antibacterial properties of GV/MB foam dressings are not entirely understood, several mechanisms have been proposed. GV and MB organic dyes have oxidation–reduction (redox) potentials in the range of many electron transport components of oxidative metabolism, and it has been suggested that these dyes operate by "short circuiting" electron transport pathways. Bacteria need a certain level of balance between reductive and oxidative actions to be able to survive. Studies have shown that GV/MB dressings alter this environment to make bacterial life unsustainable.[9,10] Both GV and MB dyes are basic with a positive charge, thus showing differential activity toward gram-negative versus gram-positive bacteria.

Effectiveness of GV/MB foams may be due in part to the preferential binding of the dyes to the

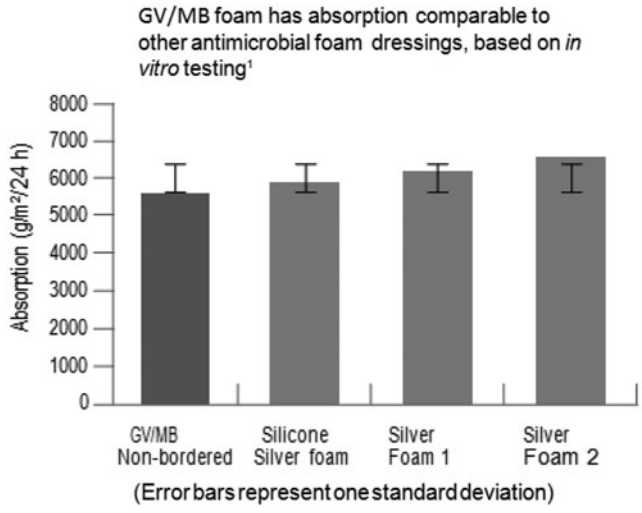

Figure 2. Absorbency of GV/MB PU foam compared to silver-impregnated and other foams.[19]Reprinted with permission from Hollister Wound Care. GV/MB, gentian violet and methylene blue; PU, polyurethane.

PVA or PU, which prevents them from washing away and becoming diluted. The bound dye presents a high local dye concentration that has been found to effectively eliminate bacteria.[10] Reduction in bacteria can result in reduced odor. Presumably, the dye transfers from the PVA or PU to the bacterial cells in contact with the dyed foam. Initial experiments showed that the dyed GV/MB foams did not support the growth of bacteria and that they eliminated living bacteria—demonstrating kill and supporting the latest bactericidal claim.[25]

GV/MB dressings work different from other antimicrobial dressings in that the foams are nonresidual and therefore do not break down and release particles into the wound bed. Rather, the antibacterial action takes place within the foam. The dyes become bound to the bacteria first before the bacteria are killed. Lab staining using high concentrations of these two dyes to identify certain strains of bacteria and viruses is representative of this activity.[9,12] Dye releases from the PVA or PU to become bound to the bacteria and is thereby only used up when needed.[9,10,12] It has been hypothesized that the dye only leaves the PVA or PU foam for more attractive proteins, bacteria, or other pathogens.[9,10,12] Although high unbound concentrations of the dyes will stain anything, small concentrations will only leave their bond with PVA for certain pathogens—thereby making the dyes selective.[9,10,12]

In contrast, with ionic silver dressings, a proportion of silver is delivered to the wound bed, which can lead to death of healthy tissue. Studies have demonstrated significant cytotoxic effects of several silver-based products on cultured fibroblasts and keratinocytes, leading to delays in reepithelialization.[7,26,27] Although most of the silver remains within the dressing or binds to proteins in the wound or wound debris, a small amount of silver is systemically absorbed during the use of ionic silver dressings.[28] Iodophors (povidone or cadexomer) have been proven to decrease bioburden, but povidone iodine is not FDA approved for the treatment of pressure ulcers, due to perceived issues with toxicity, systemic absorption, and delayed healing.[2,29] In addition, antimicrobial action of an iodophor is inactivated with heavy exudate, and it is not effective if left in the wound for more than 2 days, therefore requiring frequent dressing changes to maintain its potency. Although *in vitro* studies of cadexomer iodine have reported a lack of toxicity for human fibroblast activity,[30] there are several advisories on use of iodine dressings in various patient populations and health conditions.[31]

Bacteria and biofilms

There has been much research into biofilms and their negative effects on wound healing.[32] Microbial biofilms can be a mechanism underlying wound infection as well as failure of a wound to heal.[33] Bacterial colonies encased in an extracellular matrix in the wound bed show increased resistance to antimicrobial agents *in vivo*.[34] Properties of these surface bacterial colonies allow them to circumvent the host's immune responses, which can increase their virulence.[35] Standard wound care is ineffective when a wound has a pathogenic-type biofilm. Pathogenic biofilms are more resistant to antimicrobial agents as they have their own exoenzymes and toxins, which prolong the inflammatory response that delays healing and defines a chronic wound.[33]

Wolcott and Rhodes[23] demonstrated using biofilm-based wound management that depressing and managing the biofilms in chronic wounds can effectively convert a nonhealing wound to a healed wound. Rotating antimicrobial or antibacterial dressings every few weeks has been suggested to reduce the ability of the biofilm to adapt and adhere to the wound bed.[23] However, efficacy of biofilm-based wound management remains to be proven in a prospective randomized controlled trial compared to best practices, including removal of all wound causative factors. There have been anecdotal reports of effectiveness of GV/MB foam in penetrating and eliminating biofilm,[36] although proof of this requires extensive study not yet undertaken.

Wound assessment first

Thorough patient and wound assessments are crucial before choosing any wound management regimen, including biofilm-based wound care. Patient needs should be assessed holistically with respect to nutrition, perfusion, and comorbidities. Critical to the wound healing process is the removal of all causes of prolonged or repeated factors that compromise tissue or circulation, including pressure, repeated trauma, edema, and poor vascularization. Then, the wound bed should be evaluated thoroughly: Is necrotic tissue present? Does it need debridement? Is the wound infected or just colonized? What about the moisture balance—does the wound need added moisture or absorption of exudate, or both?[37]

Absorption

It is important to recognize that antimicrobial properties alone are not enough to determine the clinical worth of a dressing.[37] The ability to absorb wound exudate and wick infectious material away from the wound bed is of additional benefit, due to reduced number of endotoxins with the potential to impede healing.[15] Drainage absorption can potentially disrupt the bacteria's ability to attach and form a biofilm.[34] GV/MB foam dressings have been shown to absorb and hold up to 300 mL of exudate, depending on size and thickness of the foam.[38]

We have observed increased absorption with GV/MB foams, particularly compared to other foams and silver dressings; however, absorption capabilities differ between PVA and PU foams, and further controlled research is required to comparatively evaluate absorptive capacities of each of the foams. In our experience, dressings can be effectively used under compression therapy without macerating wound edges. Dressings with the moisture retentive backing can usually be left in place for 7 days underneath compression with no strike through, allowing a longer time between compression wrap changes. Results of anecdotal studies have demonstrated superior absorbency of PVA GV/MB foam dressings compared to silver-based wound dressings and other superabsorbent foam dressings,[39] as well as per dressing cost savings compared to silver-based dressings,[40] but considerably more controlled clinical research is needed to validate these findings.

Wound edge epibole

Another essential factor in wound healing is re-epithelialization. In chronic wounds, keratinocytes gathered at the wound edge may activate and form a type of callus, which inhibits the migration of these cells across the wound bed to close the wound. Different theories have been proposed to explain this phenomenon, relating to proteases, hypoxia, inflammation, and breakdown of the extracellular matrix.[41] Maintaining moist wound edges and removing toxins away from the site can help prevent rolled wound edges or epibole. GV/MB dressings can help flatten wound edges and reduce the need for sharp debridement, therefore permitting re-epithelialization,[42] as demonstrated in Fig. 3A–C.

Pain relief

Pain during treatment or dressing removal is known to decrease patient acceptability and compliance.[43] A pain study of 5,850 patients with chronic and acute wounds confirmed that dressing removal was most painful when there was adherence to the wound bed.[43] Results showed that switching to a nonadherent dressing reduced pain during dressing changes in 88% of patients with chronic wounds and 95% of patients with acute wounds. GV/MB PU and PVA foams are nonadherent to the wound bed and can be left in place for several days.[11] In a comparative study of 20

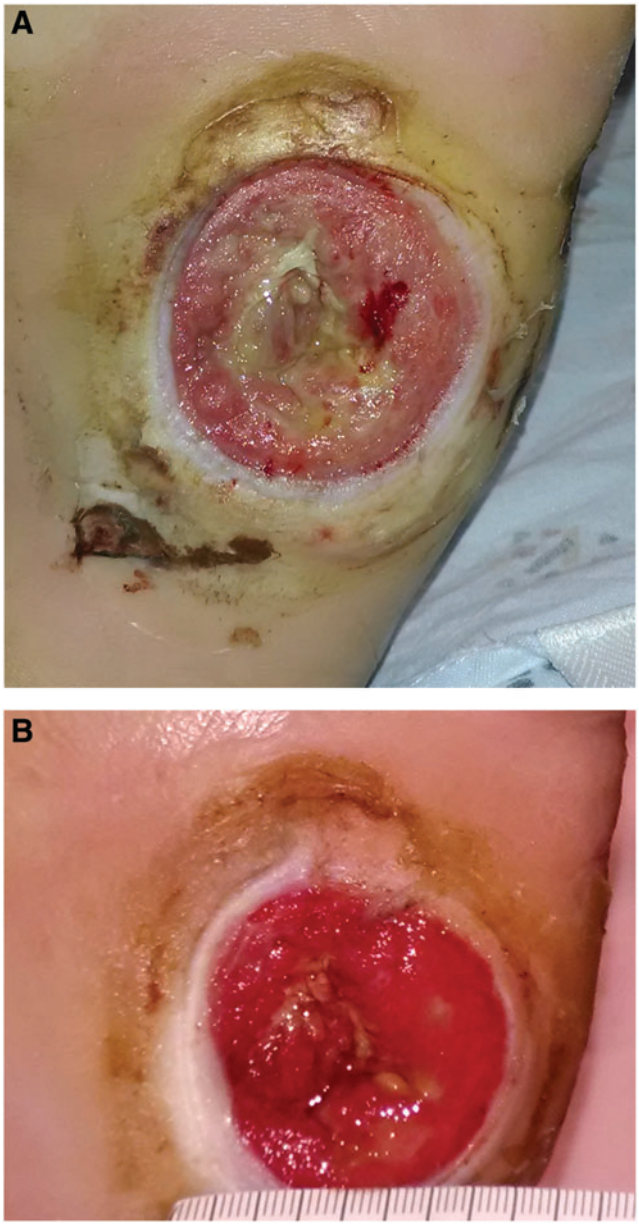

Figure 3. Chronic foot wound of 8 years duration. **(A)** A 58-year-old male with extensive cardiac history presented with chronic foot wound that had been present for 8 years. Prior treatments included fasciocutaneous flap with subsequent dehiscence and cellulitis, multiple debridements, acellular dermal matrix, negative pressure wound therapy, and split-thickness skin graft. Foot deformity had appearance of Charcot foot. GV/MB PU foam dressing was applied following sharp debridement of thick callous around rolled wound edges (epibole). **(B)** After 2 weeks, wound was 2.0 cm smaller with decreased depth, open and flattened wound edges, and healthy red tissue. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

wounds treated with GV/MB PVA foam and 20 treated with a silver-based wound dressing, an 88% pain reduction was noted in the GV/MB group versus a 40% pain reduction in the silver group.[40] The pain reduction reported by patients with GV/MB foam dressings in place[40] could be the result of hydrostatic pressure relief, similar to the effect of wet hydrogel type dressings. Absorption and retention of endotoxins may also contribute. In addition, GV is a known analgesic,[44] which may explain why patients at our facility note a reduction in pain with the dressing, but more study is required to validate this effect.

Application of GV/MB dressings

Ease of application and removal of dressing are proven factors in dressing acceptance by caregivers and patients (Fig. 4A–C).[45] We have found the GV/MB dressings relatively easy to apply and remove, with the occasional exception of the GV/MB PVA foam, which can stick on the wound bed if it becomes dried out. GV/MB dressings generally cost less than silver dressings and may require less frequent dressing changes versus other antimicrobial dressings due to absorptive capabilities.

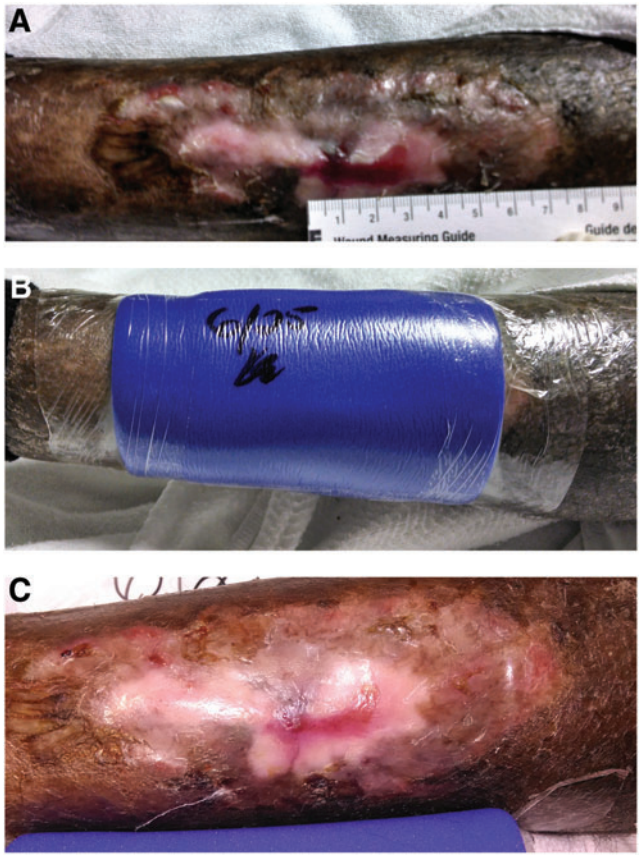

Figure. 4. Chronic leg wound. **(A)** A 47-year-old male presented with a chronic venous ulcer present for 10 months. 10×4 cm thick scab covered area. Conservative sharp debridement was performed to remove scab. Three superficial open areas remained, the largest measuring 3.0×1.0 cm. **(B)** GV/MB foam dressing applied to entire area to cover all wounds and secured with thin film around edges so patient could shower. **(C)** After 2 days of GV/MB dressings, wounds were completely reepithelialized. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

PVA versus PU: abbreviated recommendations

The type of GV/MB dressing chosen depends on the overall wound assessment, individual caregiver preference, and clinical setting. Specifically, product selection at our facility regarding GV/MB foam type is based on results of the wound assessment, required foam thickness, and need for moisture retentive backing. Following are general guidelines based on our experience:

- Hydrated PVA foam can either deliver moisture to a dry wound or absorb exudate from a draining wound, thus can be used for more than one type of wound, even on the same patient.
- GV/MB PVA foam, versus GV/MB PU foam, may be better suited for dry wounds due to its moistness.
- Dressings with moisture retentive backing are more effective underneath ostomy pouch to allow drainage absorption without undermining the seal of the wafer.
- Thinner incisional dressing may be most suitable for plantar diabetic foot ulcers due to the thinner foam resulting in greater comfort for ambulation as well as moisture barrier to protect against strikethrough.
- In large university hospitals such as ours, GV/MB PU foam may be more suitable for staff nurse use since it does not need to be hydrated, therefore removing decision-making responsibility in determining the quantity of moisture needed for each dressing. During past years in our hospital staffed by over 3,500 nurses, wound ostomy continence nurses were seeing evidence of improper use of the GV/MB PVA foam in that staff nurses were routinely applying the PVA dressings too wet, too dry, or too big—causing deterioration of the periwound and wound bed. Following mass implementation of the new GV/MB PU foam, dressings have been applied correctly on follow-up visits with improved results for healing.

TAKE-HOME MESSAGES

- Antibiotic ointments are highly selective and effective only against certain bacteria that are sensitive to that particular antibiotic.
- Antibacterial action of GV/MB dressings takes place within the foam, rather than through the release of particles into the wound bed.
- PVA-based GV/MB foam requires saline hydration, whereas PU GV/MB dressings do not.
- GV/MB antibacterial dressings can be used with enzymatic debriding agents and growth factors without inhibition.
- Absorption of excess drainage is important in reducing wound bioburden.
- GV/MB dressings have been shown to aid in autolytic debridement and to promote reepithelialization by flattening of wound edges.
- There are many other absorptive, nonadherent, and antimicrobial dressings in the wound care product market; however, a thorough product comparison is beyond the scope and intent of this article.

SUMMARY

The role of antibacterial dressings in managing colonized and critically colonized wounds requires more research to support clinical results observed by this author. Anecdotal outcomes at our facility suggest GV/MB antibacterial foams may be of particular use in colonized wounds to assist in autolytic debridement and to absorb and trap bacterial debris away from the wound. The risk of cytotoxicity is considerably reduced due to the nonresidual nature of the GV/MB-bonded dressings.

There are numerous configurations of the hydrophilic GV/MB PVA and PU foams, and dressing selection should be based on careful patient and wound assessment. In our experience, the new GV/MB PU dressings are simple to apply and best suited for moist wounds that do not require additional hydration. Both GV/MB foam dressings appear to possess the key ingredients for topical antibacterial use, including the maintenance of a moist wound environment, decreased frequency of dressing changes, and affordability. However, controlled research is needed to further define wound characteristics that would benefit most from GV/MB foam dressings.

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Abbreviations and Acronyms

ACD = allergic contact dermatitis
ARDS = acute respiratory distress syndrome
GV = gentian violet
MB = methylene blue
MRSA = methicillin-resistant *staphylococcus aureus*
PU = polyurethane
PVA = polyvinyl alcohol
VRE = vancomycin-resistant *enterococcus*