

CASE STUDY

The use of gentian violet and methylene blue impregnated foam for treatment of chronic leg ulcers

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Abstract

Chronic leg ulcers are frustrating wounds to heal. Successful treatment relies on effective diagnosis and management of the underlying aetiology of the chronic leg ulcer as well as appropriate local wound treatment. Extensive knowledge of the range of dressing products is essential to be able to source the most appropriate dressing for your patient. We present here examples of our early positive experience with a newly introduced product to Australia and its use in difficult to heal wounds. The product is gentian violet and methylene blue (GVMB) impregnated into a polyvinyl alcohol foam (Hydrofera Blue CLASSIC®, AinsCorp Pty Ltd). It has many advantages including an antibacterial effect with negative pressure wicking of bacteria, exudate and debris, long wear time and pain free removal and it is cost effective. These case reports illustrate three cases where GVMB dressings have been used successfully in chronic leg ulcer management.

Keywords chronic leg wounds, dressings, antimicrobial

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Introduction

Chronic leg and foot ulcers are a significant cause of morbidity in Australia with a point prevalence of 0.11% in one study¹. In the elderly population, chronic leg ulceration is a common recurrent problem². Numbers are likely to increase as population grows. Chronic leg ulcers provide a significant management dilemma for family physicians and specialists alike and place a strain on the Australian health system, costing an estimated A\$3 billion per year, or 2% of Australian national healthcare expenditure³.

The common aetiologies of chronic leg ulcers are venous, arterial, mixed (both arterial and venous), trauma, vasculitis, and neoplasm, although other causes exist (Box 1)^{4,5}. Effective treatment of chronic leg ulcers relies on management of comorbidities in combination with local wound treatment. Without appropriate diagnosis and treatment of the underlying aetiology, chronic leg ulcers will not heal with local treatment alone. Common comorbidities which compromise healing in leg ulcers include chronic venous insufficiency, diabetes

mellitus, hypertension, obesity, dyslipidaemia and peripheral vascular disease⁴. These comorbidities lead to patterns of wound healing which may become stagnant or prone to regular break downs. Management of comorbidities can be poorly tolerated in some patients as they may be invasive (such as varicose or endovascular surgeries or surgical revascularisation of peripheral vascular disease), uncomfortable (such as with compression therapy), or difficult to manage in some patients (such as poorly controlled diabetes mellitus, weight loss or dyslipidaemia)⁶.

Local wound treatment has challenges too. An ideal wound dressing should reduce pain and discomfort, absorb wound exudate without drying out the wound, allow gaseous exchange, protect against physical, chemical and bacterial contamination, adapt to the prevalent wound healing phase, be easy and comfortable to apply and change, be economically viable and reduce bacterial load⁶.

The impact of microorganisms on chronic ulcers has been extensively studied. Wound infection is a continuum with stages ranging from contamination (where non-proliferating

microbes are present within the wound but do not cause a host response), to colonisation (where microbes within the wound undergo limited proliferation without causing a host response), to local infection (where microbes are present in sufficient numbers or virulence to cause a local host response and impair healing), to spreading infection (where microbes invade the surrounding tissue such as muscle or fascia), and to systemic infection (where microbes from the wound affect the whole body, spreading via vascular or lymphatic channels)^{7,8}. Topical antimicrobial dressings may be required in the management of chronic wounds when individuals are at increased risk of wound infection, when local infection is present, or for local treatment of spreading or systemic infection when combined with systemic antibiotics^{9,10}.

A newly released product in Australia is Hydrofera Blue CLASSIC®. It is a combination of gentian violet and methylene blue (GVMB) impregnated into a polyvinyl alcohol foam (Box 2). Neither gentian violet (GV) nor methylene blue (MB) alone are new products, with GV discovered by French chemist Charles Lauth in 1861, and MB discovered by German chemist Heinrich Caro in 1876^{11,12}. GV has long been established as the basis of the Gram stain, with gram positive bacteria staining blue. It has had many roles as an antibacterial, antiseptic and anti-tumour agent, being used topically, intralesionally and intravenously¹¹. It has good antimicrobial effect especially against gram positive bacteria including Methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida* and the parasite *Trypanosoma cruzi* (used in blood transfusions to prevent Chagas disease), with some but lesser effect against Gram-negative bacteria. MB has had many roles such as in the treatment of malaria, as an antidote to carbon monoxide and cyanide poisoning, and is used in sentinel lymph node biopsies, Alzheimer's and bipolar disorder. These dyes are impregnated into a polyvinyl alcohol foam which, as suggested in a study by Heying in 2004, wicks bacteria laden exudate away from the wound via a negative pressure effect of somewhere between 17.8–71.2mmHg¹³. No more recent publications could be found regarding the negative pressure effect of GVMB dressing.

GVMB is not released into the wound bed but acts within the dressing. Bacteria are absorbed into the dressing and destroyed within 24 hours. The local antibacterial activity of GVMB is likely due to its ability to compromise the extracellular surface of bacterial membranes by altering their oxidative-reduction (redox) potential of oxidative metabolism, thus creating a hypoxic environment in the dressing, resulting in bacterial cell death^{14–18}.

In a poster presented by Solano-Kiedaisch et al¹⁹ at the WUWHS Congress 2008, they showed that GV was more effective (lower minimal inhibitory concentration) than silver nitrate in inhibiting gram-positive bacteria (*S. aureus* and *S. epidermidis*), and *Candida albicans*. Similar effectiveness was observed against *Proteus mirabilis*. GV was less effective than the silver nitrate against Gram-negative bacteria (*E. coli* and *Klebsiella pneumoniae*).

This study aimed to evaluate the effectiveness of GVMB dressings in the management of chronic leg ulcers which had failed to heal with alternative treatments. Three representative cases are reported. TGA approval was obtained for the use of GVMB in all patients.

Cases

Case A

Patient A was a 91-year-old male with bilateral below knee amputations for peripheral vascular disease. After using his left kneecap as a 'bumper' in his motorised wheelchair, he developed a chronic ulcer over the left patella with exposed bone. Following his presentation, Patient A underwent a flap repair of the wound. This flap repair failed, and the left patella was again exposed. The patient declined further surgery at that time and the ulcer was managed with a variety of standard moist wound healing dressings. 10 months following the initial surgery, there remained two wounds with exposed patella. He agreed to further minor surgery with a wound debridement and patella decortication and was

Box 1. Aetiology of chronic leg ulcers^{4,5}

Venous
Mixed
Arterial
Vasculitis
Neoplasm
Trauma
Pyoderma gangrenosum
Lymphoedema
Post-surgical
Drugs
Unclear/other

Box 2. Features of Hydrofera Blue CLASSIC®

Wicks exudate and bacteria into dressing via low negative pressure effect
Sequesters exudate, debris and bacteria within dressing
Broad antibacterial spectrum – bacterial cell death in the dressing
Encourages autolytic debridement
GVMB is not released into the wound bed thus: <ul style="list-style-type: none"> • Is non-toxic • Has minimal stinging or burning on contact • Will not harm growth factors etc in wound
Atraumatic pain-free removal
Excellent absorbency
Compatible with enzymatic debriding agents (e.g. Collagenase)
Colour changes (blue to white) when GVMB is depleted, indicating time to change dressing
Sustained action with twice weekly dressing changes

managed with ultra-lightweight negative pressure wound therapy (PICO®) until the wounds granulated. Wound cultures were positive for Methicillin-sensitive *S. aureus* (MSSA).

Three weeks following debridement, the patient was started on GVMB dressing covered with a polyurethane film dressing. These dressings were changed weekly with saline hydration occurring twice per week (Figure 1). After 7 weeks with GVMB dressing, the wounds had healed. 1 week later there was secondary breakdown in the lateral area and the patient was recommenced on the GVMB dressing. Despite continuing to heal, the wound developed a secondary infection 9 weeks after the GVMB dressings were restarted. Cultures were positive for *Serratia macerans* and MSSA. The patient was prescribed antimicrobials and was started on topical Bactroban ointment. Three weeks later, GVMB dressings were recommenced and within 2 weeks the wound was completely healed.

Case B

Patient B was a 63-year-old male who presented with an ulcer on his left lateral malleolus after knocking his ankle in the shower. This was on a background of a compound ankle fracture in the 1970s which was treated with a tubed pedicle flap. Conservative management was attempted with Medihoney®, Flamazine®, Sorbact®, Bactroban ointment® and Iodosorb® with limited response after 15 months. The patient was commenced on GVMB dressings covered with low adherent dressing and a bandage. The dressing was hydrated with saline and reapplied twice weekly (Figure 2). Once again, the ulcer showed a steady reduction in size and was completely healed after 4 months.

Case C

Patient C was a 38-year-old morbidly obese male with chronic bilateral leg wounds on a background of osteomalacia and multiple bilateral lower limb stress fractures as a complication of high dose steroids for asthma. He had severe bilateral peripheral oedema which, in combination with excoriation from eczema, saw him develop ulcers on his left lateral malleolus and right pretibial area. Cultures initially grew *Stenotrophomonas maltophilia* and MRSA. Ten months post-development of the ulcers he was taken to theatre for surgical debridement after which he was maintained as an inpatient for over a month. Despite trialling negative pressure wound therapy, silver dressings, Urgoclean® and Sorbact®, the ulcers continued to build up large amounts of slough with ongoing redness around the wounds. He was commenced on GVMB dressings 2 months after the debridement. The GVMB dressing was covered with absorbent pads and compression bandaging and was hydrated with saline and reapplied twice weekly. The wounds improved dramatically, with complete healing of the left lateral malleolus ulcer and nearly complete healing over the right pretibial area after 4 months (Figure 3 & 4). During the COVID-19 crisis the patient elected not to attend the clinic for follow-up or allow district nursing visits and the wound over the right pretibial

area worsened. Once lockdown restrictions were lifted he progressed again with adequate nursing care and GVMB dressings under compression.

Discussion

These case reports illustrate the successful use of GVMB dressings in chronic leg ulcer management. We have shown that GVMB dressings may be used as an alternative management strategy in chronic, non-healing ulcers. This was due to patients achieving complete or near complete healing with GVMB dressings despite numerous failed attempts with other dressings.

Many small case reports and posters have been presented on the use of GVMB dressings for acute and chronic wounds^{18,20-25}, all showing beneficial effectiveness. However, few series have been reported and most have small case numbers with only one prospective randomised controlled trial (Table 1). Coutts et al²⁶ reported 15 chronic foot/leg ulcers with bacterial load with 57% wounds improving over the 4 weeks of the observation window. Lullove²⁷ reported its use in 53 patients over ovine-based Collagen Extracellular Matrix (CECM). He attributed the ulcer healing to the CECM and stated that other foam secondary dressings were suitable and so results in this study can not be attributed to the GVMB dressing per se. A study conducted by Woo et al²⁸ which evaluated GVMB dressings for management of chronic wounds with local infection supported its antibacterial properties in the clinical setting. In this study, all 29 participants had decreased wound size, reduction in devitalised tissue and reduced infection after using GVMB dressings were applied for 4 weeks despite initial local wound infection.

Conwell et al²⁹ presented a poster reporting a prospective randomised controlled trial of 40 patients with lower leg wounds comparing GVMB dressing with Acticoat®. No statistics were presented but the GVMB dressing outperformed the Acticoat® in terms of reducing wound pain, flattening of wound edges, less maceration and more rapid healing. They showed considerable cost savings with the GVMB dressing over the silver containing dressing.

A Canadian study by Hurd³⁰ demonstrated a significantly improved wound healing outcome for a population of 6300 patients who were managed with GVMB dressings and integrated care bundles when compared to patients who were not on integrated care bundles with any dressing product. Overall, there was a reduction in healing time for the GVMB dressings and integrated care bundles compared to the control group by over 50% and significantly fewer nursing attendances/dressing changes were required. How much can be attributed to the superior management of the patient and how much to the dressing product was not evident from this paper.



Figure 1. Case A
Wound appearance pre-debridement (A, B).
Wound post-debridement and PICO® (C).
Wound appearance post-commencement of GVMB dressings at 4 weeks (D), 6 weeks (E), and 3 months (F). The wound completely healed after 5 months.

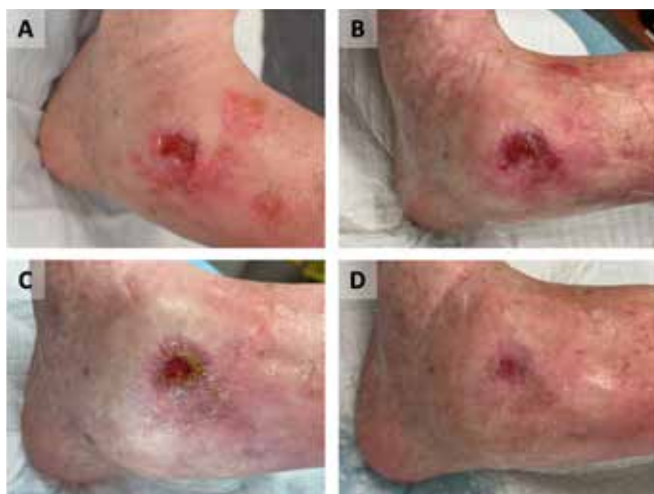


Figure 2. Case B
Wound appearance post-commencement of GVMB dressings at 3 weeks (A), 5 weeks (B), 9 weeks (C), and 11 weeks (D). The wound completely healed after 4 months.

The limitations of this study and many of those reported are those that inherently affect any case reports and series. Interpretation of results may be limited by the lack of a control group, low case numbers, heterogeneity of participants and the single institution setting. Outcomes reported frequently reflect the senior author's experiences. These limitations may affect the generalisability of these results. Further research is required in the form of multicentred randomised controlled trials in which GVMB dressings are compared with other dressings after a period of incomplete wound healing.



Figure 3. Case C – right pretibial area
Wound appearance post-commencement of GVMB dressings as 1 week (A), 1 month (B), 2 months (C), 2 months with dressing in situ (D), 3 months (E), and 4 months (F). Recurrence with COVID-19 isolation (G). Wound nearly completely healed 5 months post-recommencing adequate GVMB dressings under compression (H).

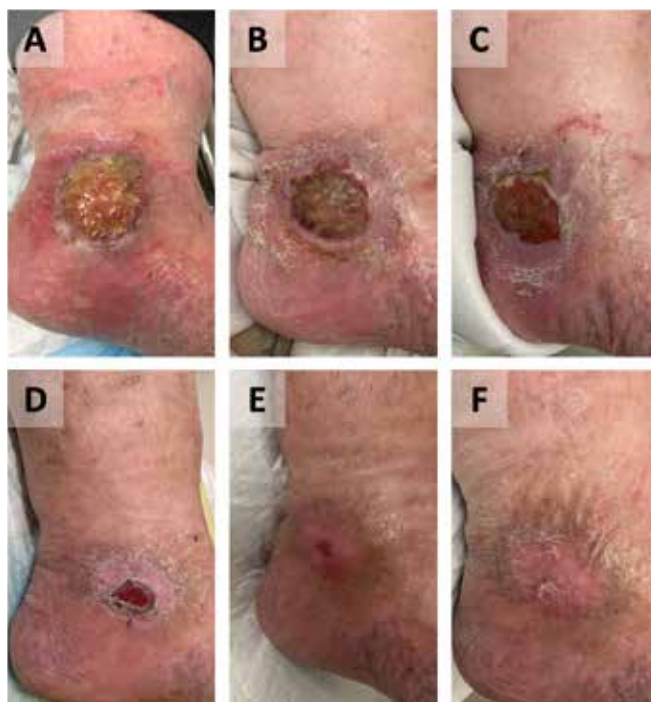


Figure 4. Case C – left lateral malleolus
Wound appearance pre-GVMB dressings (A). Wound appearance post-commencement of GVMB dressings at 1 week (B), 1 month (C), 2 months (D), 3 months (E) and 4 months (F).

Table 1. Review of other studies

Study	Case numbers	Outcomes
Coutts et al (2014) ²⁶	15 patients with chronic foot/leg ulcers treated with GVMB dressings	Outcomes at week 4: <ul style="list-style-type: none"> • Complete healing (n=1) • Decreased wound size (n=8) • No change to wound size (n=1) • Increased wound size (n=5)
Lullove (2017) ²⁷	53 patients with chronic foot/leg ulcers treated with ovine-based collagen extracellular matrix and GVMB dressings	Outcomes at week 12: <ul style="list-style-type: none"> • Complete healing (n=31) • Reduction in wound size by >80% (n=12) All wounds completely healed at week 24
Woo et al (2017) ²⁸	29 patients with chronic ulcers treated with GVMB dressings	Outcomes at week 4: <ul style="list-style-type: none"> • Mean wound surface area reduced by 42.5% (p<0.05) • Mean wound surface area covered with devitalised tissue reduced by 78.3% (p<0.05) • Mean PUSH score decreased by 19.5% (p<0.05) • Mean wound infection score (UPPER and LOWER wound infection checklist) reduced by 75% (p<0.05)
Conwell et al (2004) ²⁹	40 patients with chronic foot/leg ulcers 20 patients treated with GVMB dressings 20 patients treated with Acticoat®	Average days to complete healing: <ul style="list-style-type: none"> • GVMB dressings (67 days) vs Acticoat® (75 days) • No statistical comparison presented
Hurd et al (2019) ³⁰	6300 patients with chronic ulcers treated with GVMB dressings and integrated care bundles compared to patients treated with any dressing and no integrated care bundles	Mean healing time accelerated by more than 50% in GVMB dressings and integrated care bundle group compared with patients treated with any dressing and no integrated care bundle

The secondary dressing over the GVMB dressing can be altered depending on the exudate level of the wound. Before applying, Hydrofera Blue CLASSIC® is hydrated with water or saline. If the ulcer has low exudate levels, it can be covered with a film dressing. If there are moderate to high exudate levels, a non-adherent dressing or absorbent pad may be used as a secondary dressing to absorb excess exudate. It may be used under compression. It is therefore very versatile in that it can be used for any wound exudate level and adjusted as exudate levels change by utilising alternative secondary dressings. It actively absorbs exudate, thereby reducing wound maceration and removing harmful bacteria that may lead to overt wound infection. It is recommended that the dressing be changed twice weekly, though we have left it on for up to 7 days in some cases (e.g., Case A). The dressing will signal when it needs changing as the blue colour changes to white as the supply of GVMB is exhausted.

There are numerous existing antimicrobial dressings; however, general superiority of one particular wound dressing over another has yet to be demonstrated^{10,31}. One product will often work brilliantly in one patient's wound but not in another. Ultimately, appropriate dressing choice comes down to cost, frequency of dressing change, who is doing the dressing, wound bed and exudate level, and then often trialling a dressing to see if it works! If there is

no improvement in the wound after 2 weeks a change to an alternative product should be considered. GVMB dressing is certainly a useful antibacterial dressing product that you may consider adding to your selection process.

Conflict of interest

The authors have no conflicts of interest to disclose.

Ethics statement

Fully informed patient consent was obtained.

Funding

Dressings were obtained under the TGA special access scheme. Dressings were donated by AinsCorp Pty Ltd to the patients, but this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contribution

AS: Manuscript write-up and collection of data. LE: Manuscript write-up and collection of data. PT: Study supervisor.

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