A clinical case series on the effectiveness of an enhanced ionic silver hydrofiber dressing in the management of diabetic foot ulceration

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Foot ulceration as a consequence of diabetes is well known and can ultimately lead to lower-extremity amputation. Biofilm is a well-defined concept in the literature and its role in the cause of human bacterial infections is well described. Clinicians now acknowledge the role of biofilm as causing delay in the healing of chronic wounds, however, this is not widely described in the literature nor included in guidelines for practice. Bacterial species that are present in biofilm are also known to exhibit tolerance to methods of antimicrobial eradication whether local or systemic. An enhanced ionic silver hydrofiber dressing (AQUACEL Ag+ Extra [AQAg+]) has been shown to disrupt biofilm *in vitro*. In this study, 10 participants with chronic diabetic foot ulceration were opportunistically recruited from the podiatry-led diabetic foot clinic in a large tertiary referral centre. AQAg+ was used on each of the participants based upon local wound assessment at each review in line with the clinic's standard treatment practice; the average length of use was 4 weeks. Clinicians were asked to consider the effectiveness of the product in managing the microbial load, exudate, and promoting healing in these patients. The results show that AQAg+ was successful in achieving the aims and was also well tolerated by patients. There is a potential for this dressing to accelerate healing in the management of diabetic foot ulcers that show signs of increased bacterial load and delayed healing.

Diabetes is a life-limiting condition, which is characterised by the presence of persistent hyperglycaemia. Such hyperglycaemia can lead to a number of complications, including foot ulceration secondary to peripheral arterial occlusive disease (PAOD) and peripheral polyneuropathy (PN). The combination of PN and PAOD increase the susceptibility of the patient to infection (Paulson et al, 2018).

Given that infection is often the reason for lower-limb amputation, the control of infection both locally and systemically is important in preventing amputation and promoting healing (Paulson et al, 2018). Kosinky and Lipsky (2010), Lipsky et al (2012) and Peters and Lipsky (2013) report that the clinical signs of infection can be absent in patients with diabetes due to the following factors; immunopathy, neuropathy, peripheral arterial disease (PAD) and hyperglycaemia. The presence of biofilm is now widely acknowledged as causing delay in the healing of chronic wounds (Metcalf and Bowler, 2013). Bacteria in a biofilm are also known to be tolerant to most topical methods of antimicrobial eradication (Malik et al, 2013).

Biofilms are surface-attached microbial communities, which are within, and protected by, a matrix of self-produced extracellular polymeric substance (EPS) or slime, which in the human body may also contain host components. Within the EPS matrix, the microorganisms are offered protection from host and external antimicrobial action; biofilm can, therefore, contribute to the failure of traditional management strategies by delaying granulation tissue formation, keeping the wound in a persistent inflammatory state, and preventing systemic and local antimicrobials from reducing the bioburden

Citation: Wilson P, Gillen C, Hughes M (2018) A clinical case series on the effectiveness of an enhanced ionic silver hydrofiber dressing in the management of diabetic foot ulceration. *The Diabetic Foot Journal* 21(4): 239–46

Article points

1. Biofilm delays healing in chronic wounds including diabetic foot ulcers.
2. Biofilm is not able to be clinically detected in chronic wounds including diabetic foot ulcers.
3. A biofilm based management strategy may be augmented by the use of AQAGx+.

Key words

- Biofilm
- Diabetic foot ulceration
- Enhanced ionic silver hydrofiber dressing

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Page points

1. Lack of a point of care test to diagnose biofilm clinically.
2. Management of suspected biofilm in chronic wounds is clinically challenging.
3. Patients with diabetic foot disease have many comorbidities.

in these wounds (Philips et al, 2010; Leaper et al, 2012).

In the diabetic foot, there is a paucity of data suggesting which topically applied treatments for the management of local bioburden are of benefit. Cochrane Reviews on this issue show a lack of robust data to advise clinicians in selecting topically applied antimicrobial agents (Bergin and Wraight, 2006; Dumville et al, 2015; Wu et al, 2015). Topical agents that reduce the bacterial load in chronic wounds are often ineffective against biofilm (Davis, 2006). It has been shown that while up to 90% of diabetic foot ulcers have biofilm in the wound, it is not possible to visualise this within the wound bed (Bowen and Richardson, 2016).

Given that there is no point-of-care test to detect biofilm clinically, the use of any strategy to reduce biofilm in any chronic wound will need to be made at the discretion of the clinician. Published literature reviews have shown the healing delay caused by biofilm, and methods of biofilm management, *in vivo* (Metcalf and Bowler, 2013). Topical antimicrobials, which have been shown to be effective in reducing the bioburden in chronic wounds by the destruction of planktonic bacteria, are less effective at destroying biofilm (James et al, 2008). Current literature suggests that biofilm should be disrupted by regular sharp debridement, vigorous cleansing and topical antimicrobial agents (Wolcott, 2015). The challenge for clinicians today when managing biofilm is trifold: the presence of biofilm on the surface of a wound is hard to detect because it is often not visible with the naked eye (White and Cutting, 2012; Metcalf and Bowler, 2014); the removal of biofilm can be challenging without disturbing delicate granulation or epithelialising tissue; and biofilm reforms very quickly, with some studies showing biofilm re-formation within 24 hours of sharp debridement (Leaper et al, 2012).

AQAg+ is comprised of sodium carboxymethylcellulose (SCMC; Hydrofiber®) with 1.2% ionic silver, with the addition of ethylenediaminetetraacetic acid (EDTA), a metal chelator, and benzethonium chloride (BEC), a surfactant (Bowler and Parsons, 2016). Metal chelators have been shown to disrupt biofilm via metal ion sequestration *in vitro* (Banin, 2006), and surfactants have been shown to disrupt the formation of biofilm *in vitro* (Dusane, 2008). SCMC is widely used in clinical practice for the management of exudate in wound promoting moist wound healing. Walker (2002) showed that the *in vitro* properties of SCMC supported the sequestration of bacteria and maintained moist wound healing, which was described as the optimal environment for wound healing by Chang (1996).

The use of silver is also well established as having effective biocidal properties in wounds (O'Neill et al, 2003). The intentions of this dressing are to absorb exudate via the SCMC, to kill bacteria via the ionic silver, and for the new components, EDTA and BEC, to disrupt biofilm, allowing the ionic silver to destroy the then-exposed bacteria. This enhanced ionic silver dressing, AQAg+, has been shown to disrupt biofilm *in vitro* (Said et al, 2014; Bowler and Parsons, 2016; Parsons et al, 2016) and *in vivo* (Parsons et al, 2013). Effective management of local bioburden also has the potential to reduce the number of systemic infections. Systemic antimicrobial treatment of wounds can prove problematic in the patients with diabetes due to the other complications of the diabetes, including chronic kidney disease, which means that the necessary therapeutic dose cannot always be delivered due to reduced renal function, as well as poor perfusion (Matzke et al, 2011).

The primary aim of this case series was to investigate the role of AQAg+ in the management of DFUs with clinical signs of local infection or possible biofilm (Cutting and Harding, 1994; Metcalf et al, 2014), the ability to manage exudate, and promote healing.

Methodology

Ten participants were opportunistically recruited from the podiatry-led diabetic foot clinic in a large urban tertiary referral centre. Approval was granted for the study by the institutional review panel who deemed that full ethical approval was not warranted. Patient information was provided about the study on an individual basis with the opportunity to ask questions with the treating clinician and other members of the investigating team. This verbal information was supplemented by written information. At the time of informed consent being obtained from each participant, digital photographs were taken of the reference wound.

AQAg+ dressings were used by a member of the investigation team at each assessment and dressing change. Additional dressings were supplied to the patient for instances when they may need to attend other services for wound review to ensure consistency of use. Digital photographs were taken at each dressing change. AQAg+ continued to be used at the clinician's discretion based upon local protocols. In order to integrate with standard clinical practice, no fixed time limits were placed on the use of the product. Participants were included with the following criteria:

- Ulcer of a diabetes-related origin somewhere on their foot with local signs of infection (Cutting and Harding, 1994)
- Possible biofilm (Metcalf et al, 2014) based on clinical judgement and augmented by secondary signs of infection (Cutting and Harding, 1994)
- Stagnant healing defined as no improvement as expected when standard care was implemented in full for 4 weeks or more.

Participants were excluded with the following criteria:

- Patients who were unable to attend for review with a member of the investigation team
- Severe vascular disease characterised by absent pulses or an ABI of less than 0.5
- Systemic infection including acute osteomyelitis of the foot, spreading cellulitis or systemic signs of infection requiring parental antibiotics
- Hospitalisation for foot-related management.

Results

The results of this study are summarised in *Table 1*. The mean duration of wounds prior to inclusion was 326 days (range 0–1, 356 days). All of these patients had significant comorbidities and were clinically challenging. At inclusion of the study, seven of the cases had confirmed chronic osteomyelitis diagnosed clinically and corroborated by MRI imaging (Lipsky et al, 2016). Of these seven patients, all had received an extended inpatient stay for the treatment of osteomyelitis with intravenous antibiotics prior to inclusion in the study. The average length of stay in these cases was 21 days (data not shown). The remaining three participants had not required prior hospitalisation at the start of the study. Of these three remaining participants, two had previously received courses of systemic antibiotic therapy prior to inclusion in the study as outpatients.

Overall, the mean number of AQAg+ dressing changes was 12 and there was no difference in number of dressing changes between those with (average 12; range 6–22) or without osteomyelitis (average 14; range 9–21). No additional dressing changes occurred in this study compared to normal standard practice.

Healing outcomes at the time of writing were as follows: five of DFUs were healed; four of patients had undergone surgery for removal of infected bone. At this point, these cases were removed from the study as per the exclusion criteria. In such cases wound healing would not be expected to occur until the underlying pathology was removed. In these 4 cases this was osteomyelitis. The remaining patient was hospitalised for the management of myocardial infarction and subsequently died.

The primary aim of this case series was to investigate the role of AQAg+ in the treatment of DFUs with local clinical signs of infection (Cutting and Harding, 1994), possible biofilm (Metcalf et al, 2014), or lack of progression towards healing. Clinicians and patients reported a reduced number of systemic infections and fewer antibiotics were prescribed in this cohort than had been previously observed.

The secondary aims were to investigate the role of AQAg+ in exudate management, standard of skin integrity and management of periwound skin. Patients and clinicians observed improved skin integrity, exudate management and periwound skin protection during the use of the product. *Figures 1–3* show wound images from patients 1, 2 and 9 at week 0 and again at the cessation of the use of AQAg+, which show a reduction in wound size over the duration of the use of AQAg+, a reduction of local signs of infection, maintenance of periwound skin integrity, and an absence of periwound maceration suggesting adequate exudate management.

Discussion

Patients with DFUs have many comorbidities. Diabetes, which leads to the presence of POAD, leads to reduction in oxygen and nutrient transportation giving rise to subsequent tissue

Table 1. Summary of study results.

Patient No.	OM?	Abx. prior?	Start date	Finish date	Duration (weeks)	Number of AQAg+ treatments	Abx during	Healed?
1	Yes	Yes	October 22	February 3	15.0	22	No	No
2	No	Yes	November 17	January 14	8.6	21	No	Yes – January 20
3	Yes	Yes	December 1	December 19	2.7	6	No	No
4	Yes	Yes	November 21	January 16	8.3	11	Yes	Lost to follow up
5	Yes	Yes	December 30	March 30	13.0	13	No	No
6	Yes	Yes	December 30	April 22	16.3	10	Yes	No
7	No	No	January 21	February 9	3.0	11	Yes	Yes — February 24
8	No	Yes	February 17	March 27	5.6	9	No	Yes — April 21
9	Yes	Yes	February 18	May 5	11.0	12	No	No
10	Yes	Yes	March 16	May 20	9.4	9	No	No
Average	7 yes (OM)	9 yes (Abx)			9.3 (3.0–16.3)	12 (6–22)	3 yes	3 yes (healed)

OM = osteomyelitis; Abx = systemic antibiotics.

hypoxia and reduced tissue penetration of any systemic therapy. Topically applied antimicrobials would have benefit as microbials thrive in the presence of tissue hypoxia. Some of the participants went on to develop further systemic complications. The presence of osteomyelitis continues to complicate management of DFUs. Diagnosis of infection is primarily a clinical diagnosis (Lipsky et al, 2016). The use of AQAg+ in this study has been partially successful in this 10-patient cohort. The study had two aims: firstly, to see if the use of AQAg+ would progress stagnant wounds towards healing, disrupt biofilm, and deal with local clinical signs of possible infection; secondly, to see if it managed exudate, protected periwound skin and maintained skin integrity.

In relation to the first aim, the results show that in the three participants without osteomyelitis the wounds healed without the need for antibiotics in two cases despite the wounds showing signs of local infection and/or biofilm in the opinion of the clinicians. In these three cases, the average number of applications was 13.6 (range 9–21). It is interesting to note that in these three cases, two participants had undergone previous courses of antibiotics. Antimicrobial resistance is a major concern in the 21st century with programmes in place to optimise the use of antimicrobials (Charani and Holmes, 2013). The importance of all healthcare professionals in antimicrobial stewardship irrespective of prescribing ability cannot be underestimated (Cahrani and Holmes, 2013). The author's experiences in this study showed that the disruption of suspected biofilm by the AQAg+ dressing has assisted in reducing the bioburden in wounds that showed no systemic clinical signs of infection. The potential for local management of infection is something that warrants further investigation especially in the absence of systemic symptoms.

The role of biofilm in DFUs is one that warrants further investigation. Evidence suggests that biofilm is a larger problem than previously reported, although the majority of these studies are conducted *ex vivo* with scanning electron microscopy (SEM) to identify the presence of biofilm in the sample (Oates et al, 2014). The use of SEM in routine

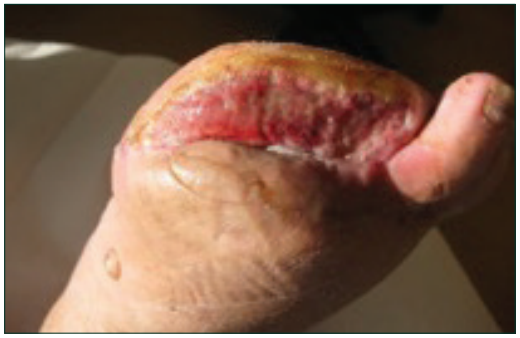

Figure 1a. Patient 1 at week 0.

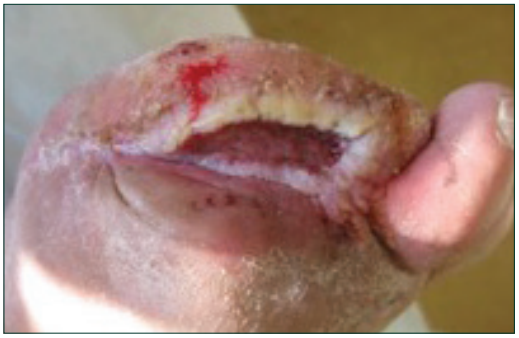

Figure 1b. Patient 1 at the cessation CMCAg+ use at week 15.

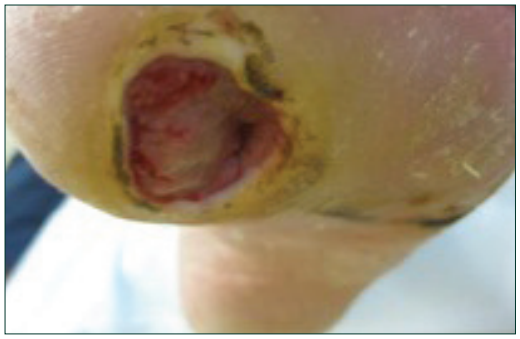

Figure 2a. Patient 2 at week 0.

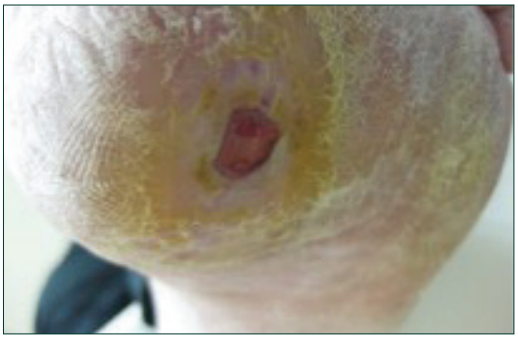

Figure 2b. Patient 2 at the cessation CMCAg+ use at week 8.

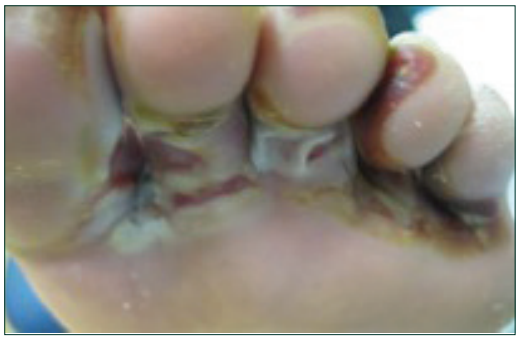

Figure 3a. Patient 7 at week 0.

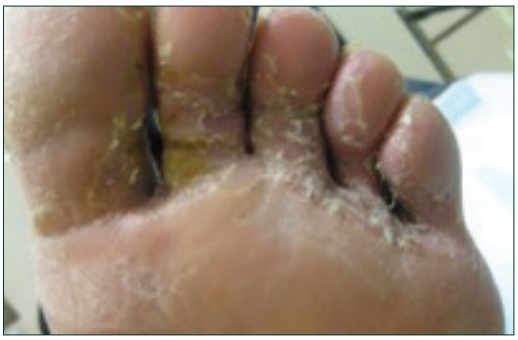

Figure 3b. Patient 7 at the cessation CMCAg+ use at week 3.

clinical practice in this way is unrealistic. It is unknown whether the use of AQAg+ in wounds where no biofilm is present has a detrimental effect on the wound. Current practice and guidelines recommends the use of topical antimicrobials only where increased bioburden is observed (Gottrup et al, 2013). This presents a challenge in the diabetic foot as the cardinal signs and symptoms of infection are absent or reduced and clinical signs of biofilm are difficult to observe (White and Cutting, 2012; Metcalf et al, 2014).

In DFUs, in the absence of point of care testing for biofilm, it is increasingly difficult for clinicians to make the correct judgement regarding the presence of biofilm. There is a clear need for a point-of-care test to assist clinicians in deciding whether there is biofilm present in wounds. Algorithms have been suggested (Metcalf et al, 2014), but these are as yet widely untested (Hurlow et al, 2016), and clinicians and scientists are divided as to whether biofilm may sometimes be seen in a wound. In the absence of knowing whether a wound bed is contaminated by a biofilm, it is challenging to draw any conclusion from the application of biofilm-based wound management.

In this study, the author considered wounds that had been stagnant for a period of time within the context of standard diabetic foot management

in situ. It is the author's experience that AQAg+ is beneficial in these wounds, and we noted a fall in numbers of systemic infections and admissions in this cohort. However, the numbers are too small to make any comments on the significance of this, and the data is largely anecdotal. Given the unpredictable nature of DFUs and their potential to deteriorate, further studies are warranted. In the author's opinion, the use of AQAg+ has been beneficial in the cases presented in this article. Clinicians reported significant improvement within one application in wounds where no previous signs of infection or biofilm had been noted on clinical assessment. In none of these cases had systemic inflammatory responses been noted. As this is a multifaceted product encompassing four elements (exudate management, ionic silver, and two anti-biofilm components), it is difficult to ascertain which variables have led to the improvements noted in these cases.

Limitations of study and suggestions for further research

This study is limited by its convenience sample as the patients were recruited based upon the opinion of the clinician and not by any method of randomisation. There was no blinding or matching in the study cohort, both the clinician and the patient were fully aware of the study being undertaken. The sample size is very small and affects one wound type in one centre.

The author suggests that further studies are undertaken to look at the effect of the use of AQAg+ on a wider cohort of patients and wound types using a systematic methodology with a larger sample. Further studies should be undertaken to look at the health economics of this product. A further driver for the use of this dressing, and indeed other antimicrobial products in wound care, may be an effective test of whether or not and where biofilm is present in wounds. Further studies need to be conducted to work on a point-of-care test for clinicians to be able to ascertain whether biofilm is present in the wound bed of any chronic wound to enable them to direct more effective practice.

Conclusion

The results of this small case series in the use of AQAg+ for chronic DFUs suggest that the dressing is effective in managing exudate, suspected biofilm and bioburden in DFUs. The potential for cost-benefit analysis in terms of reduction in admission, surgery and reduction in the use of systemic antibiotics warrants further investigation. The product was well tolerated by patients and clinicians found it easy to use. AQAg+ is now used as standard practice in our centre and the authors recommend its consideration in the management of DFUs where clinicians require a product that combines moist wound healing, absorbs exudate, has antimicrobial actions and where they are suspicious that the presence of biofilm may be a contributory factor in delayed healing. ■

Declaration

AQAg+ dressings were supplied for the purposes of this study by the manufacturer without direct cost to the investigation team.

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